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(54) **METHOD OF PRODUCING STRUCTURES USING CENTRIFUGAL FORCES**

VERFAHREN ZUR HERSTELLUNG VON STRUKTUREN DURCH GEBRAUCH VON ZENTRIFUGALEN KRÄFTEN

PROCEDE PERMETTANT DE PRODUIRE DES STRUCTURES A L'AIDE DE FORCES CENTRIFUGES

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- **PATENT ABSTRACTS OF JAPAN vol. 018, no. 557 (P-1817), 24 October 1994 (1994-10-24) & JP 06 202087 A (SUMITOMO ELECTRIC IND LTD), 22 July 1994 (1994-07-22)**
- **PATENT ABSTRACTS OF JAPAN vol. 013, no. 589 (C-670), 25 December 1989 (1989-12-25) & JP 01 247435 A (SEKISUI CHEM CO LTD), 3 October 1989 (1989-10-03)**

Description

FIELD OF INVENTION

[0001] This invention relates to a process of producing a product, in particular to a process of manufacturing structures and particularly polymeric tubular structures with complex and unique morphologies in the walls, and on the inner and outer surfaces of the structures.

BACKGROUND OF THE INVENTION

[0002] Tubular structures have been prepared by a number of techniques, each of which has limitations for each application. For biomedical applications, a limitation is the abundant material required to prepare structures of limited size and shape, which can prove costly. For porous polymeric tubes, also known as hollow fiber membranes (HFMs), tubes with wall thicknesses on the order of hundreds of microns are prepared. There is no suitable method to prepare concentric, long HFMs, with thin walls, whether by dip-coating, spinning, or centrifugal casting, among others. As will be described in more detail, the invention comprises a process to prepare HFMs, or any hollow structure, with a broad range of wall and surface morphologies, dimensions and shapes. Such wall morphologies allow HFMs to be manufactured with considerably different transport properties while maintaining similar mechanical properties.

[0003] HFMs are commonly prepared by phase inversion through an annular die (or spinneret) where the solvent/non-solvent system controls many of the resulting properties, such as morphology of the wall structure. The dimensions are controlled by the spinneret, which must be finely tuned for concentricity. While the spinning technique has a proven record commercially, it requires abundant material and requires a certain amount of art to prepare reproducible HFMs.

[0004] Centrifugal casting is a process used to make a wide number of structures, both tubular and non-concentric (United States Patent Nos. 5,266,325; 5,292,515). For manufacturing tubular shapes, a cylindrical mold is partially filled with a monomer, polymer melt, or monomer solution, and with air present inside the mold, coats the periphery of the mold under centrifugal action. The material spun to the outer portion of the mold is then held in place using temperature changes (cooling), polymerization or evaporation of the solvent For this process, two phases are present inside the mold (air and liquid) before rotation; phase separation is not necessary for tubular formation. Wall morphologies are only attained by the addition of a porogen (salt, ethylene glycol etc.) that is leached out post-polymerization. Since air is required in the mold to form a tube (compared to a rod), attaining small diameter tubes with a small inner diameter on the micron scale cannot be achieved. Surface tension between the liquid and the gas inside the mold prevents miniaturization of the inner diameters for tens of centimeter length tubes.

[0005] For dip-coating, tubes are formed around a mandrel that is sequentially dipped in a polymer solution and non-solvent system, thereby coating the mandrel with the polymer via a phase inversion process. Alternately, the mandrel may be dipped in a polymer solution and the solvent left to evaporate. By these methods, the uniformity of the tube wall along the length of the tube is not well controlled.

[0006] There have been other well-known methods of producing different structures by using centrifugal force and phase separation,

[0007] Patent Abstracts of Japan, vol. 018, no. 557 (P-1817). 24 October 1994 & JP 06 202087 A (Sumitomo Electric Ind Ltd) is directed to a method for producing a composite film of uniform transmittance. The method includes dissolving a high-polymer material and a liquid crystal material in a low boiling solvent to prepare a coating liquid, which is then applied on a substrate. The coated substrate is placed in a gaseous flow of gaseous nitrogen, or is rotated to evaporate the solvent. The coated surface is smoothed by the wind force of the gaseous flow or the centrifugal force generated by rotation, thereby producing a structure wherein the polymer and liquid crystal materials are finely separated in phase.

[0008] U.S. Patent No. 5,250,240 to Kim et al. teaches an economically way of producing a hollow, fibrous, porous separation membrane from polyolefins by thermally induced phase separation. The process comprises spinning a melt blend solution of a polyolefin of a certain melt index in a diluent selected from the group consisting of natural soybean oil, pure linoleic acid, and a mixture of oleic acid, linoleic acid and palmitic acid to form a hollow, fibrous, porous, polyolefin separation membrane; extracting out the diluent followed by coagulating the membrane with a coagulating and extracting solvent; and evaporating out the solvent together with any residue of the diluent.

[0009] Patent Abstracts of Japan, vol. 013, no. 589 (C-670), 25 December 1989 & JP 01 247435 (Sekisui Chem Co Ltd) discloses a method of producing a porous objection without using any solvent The method includes heat-treating an intimate mixture of a linear aromatic polyether sulfone and poly(2-oxazoline) to a specified temperature range to effect phase separation of these two polymers in the state of continuous phases. The mixture is then cooled to the glass transition temperature or below, and the poly(2-oxazoline) is extracted with water to produce a porous object.

[0010] UK Patent Application, GB 2 003 108 A (Sandoz Ltd) is directed to a method for producing microspheres of a core material and a polymer by using a low temperature phase separation step. The method comprises adding a phase separation agent to a medium comprising a solution of the polymer and a solution or dispersion of the core material at

a temperature of -40 °C to -100 °C. This patent application teaches that the low temperature phase separation step prevents uncontrolled agglomeration of the microspheres.

[0011] DE 15 14 410 (Siemens Schuckert Werke AG) discloses a rotational structure, such as a magnetic circular disc suitable as pulse transmitters for digital angular step resolvers. The rotational structure is produced by filling a rotational mold with a mixture of casting resin and a comminuted magnetizable filler material, and heating the mixture in the mold to maintain its fluidity while centrifuging until the filler material is driven to the peripheral marginal zone where it becomes uniformly distributed along the periphery. Thereafter, the mixture is hardened by permitting it to cool down to normal room temperature.

[0012] It would therefore be very advantageous to manufacture tubes within a size regime, concentricity and with a multi-layering capability that is not presently achievable with the aforementioned methods.

SUMMARY OF INVENTION

[0013] It is the object of the present invention to provide a method of manufacturing a variety of structures, such as, but not limited to, polymeric tubular structures, which enables wall and surface morphology, dimension and shape of the structures to be easily controlled.

[0014] This object of the present invention can be achieved by the process of producing a product comprising

a) filling an interior of a mold with a solution so that substantially all air is displaced therefrom, the solution comprising at least two components which can be phase separated by a phase separation agent into at least two phases;
b) rotating said mold containing said solution at an effective rotational velocity in the presence of said phase separation agent to induce phase separation between said at least two components into at least two phases so that under rotation at least one of the phases deposits onto an inner surface of the mold; and
c) forming said product by stabilizing said at least one of the phases deposited onto the inner surface of the mold.

[0015] Particular embodiments of the invention are the subject of the dependent claims.

[0016] The product formed by this process may be removed from the mold, or alternatively remain in the mold where the product and the mold are used for various applications. The product may be a polymeric material, in which case the solution includes either monomers or polymers or both.

[0017] The product may have a wall morphology that includes a porous structure, a gel structure or overlapping regions of porous/gel structure.The polymeric product may have a wall morphology that includes a predominantly gel morphology with porous channels running from a periphery to a lumenal side, resulting in spotting on an outer wall surface.

[0018] The polymeric product may be a multi-layered product produced by repeating steps a), b) and c), at least once to produce a multi-layered product.

[0019] The polymeric product may be used as a reservoir for the delivery of drugs, therapeutics, cells, cell products, genes, viral vectors, proteins, peptides, hormones, carbohydrates, growth factors.

[0020] The polymeric product may contain microspheres containing preselected constituents, and wherein the product includes said microspheres distributed either uniformly or in a gradient within the wall structure of the product.

BRIEF DESCRIPTION OF DRAWINGS

[0021] The following is a description, by way of example only, of the method of producing tubes in accordance with the present invention, reference being had to the accompanying drawings, in which:

Figure 1a is a cross section of a cylindrical mold used to manufacture tubes according to the present invention;
Figure 1b is a cross section of an alternative embodiment of a cylindrical mold;
Figure 1c is a cross section of another alternative embodiment of a cylindrical mold;
Figure 1d is a cross section of another alternative embodiment of a cylindrical mold;
Figure 2a is a cross section of an embodiment of a cylindrical mold with surface features along the length of the interior surface of the mold;
Figure 2b is a cross section of an alternative embodiment of a cylindrical mold with surface features along the length of the interior surface of the mold;
Figure 2c is a cross section of another alternative embodiment of a cylindrical mold with surface features along the length of the interior surface of the mold;
Figure 2d is a cross section of another alternative embodiment of a cylindrical mold with surface features along the length of the interior surface of the mold;
Figures 3a to 3c shows the steps of filling a cylindrical mold with a liquid, Figure 3a shows the puncturing needle (D) is used to allow exit of air from the mold, while a syringe filled with solution (E) is injected through a needle (C)

that punctures the lower injection port; Figure 3b shows the filling of the mold with the liquid solution, air exits needle (D) as the solution fills the mold, and Figure 3c shows the mold completely filled with solution with the visible air all displaced;

Figure 4a shows a method of rotating the cylindrical mold in which the filled mold (A) is inserted into a drill chuck (F) and rotation of the mold is commenced;

Figure 4b shows another method of rotating the cylindrical mold in which the filled mold (A) is attached to the two ends of a lathe (G) and rotation of the mold is commenced;

Figure 4c shows another method of rotating the cylindrical mold in which the filled mold (A) is inserted into an adapter (H) so it can be placed into a drill chuck (F) and rotation of the mold is commenced and wherein O-rings (I) maintain position of mold (A) inside the adapter (H);

Figure 5a is a perspective view showing a mold (A) filled with a liquid mixture (E) rotated about an axis at a suitable speed to centrifuge the phase that will eventually separate;

Figure 5b shows the mixture (E) of Figure 5a beginning to phase-separate during rotation, the dense phase (J) is centrifuged to the periphery of the mold where it adopts the shape of the inner surface of the mold (K);

Figure 6 shows an environmental scanning electron microscope (ESEM) micrograph of a gel-like coating on the inside of a glass mold; produced with the mixture formulation of 1% HEMA, 99% water, 0.01 %APS, 0.01 % SMBS, 4000 rpm (also listed in Table 1 as example 1);

Figure 7a shows a scanning electron microscope (SEM) micrograph of the outer surface of a porous coating applied to the inside of a glass mold, produced with the mixture formulation of 1.9% HEMA, 0.1 % PEGMA, 98% water, 0.02% APS, 0.02% SMBS, 2700 rpm (also listed in Table 1 as example 2);

Figure 7b shows a SEM micrograph of the inner surface of a porous coating applied to the inside of a glass mold, produced with the mixture formulation of 1.9% HEMA, 0.1 % PEGMA, 98% water, 0.02% APS, 0.02% SMBS, 2700 rpm (also listed in Table 1 as example 2);

Figure 8a shows a porous plug (L) is included within the mold of Figure 5a prior to the injection of a liquid mixture; after phase separation and gelation, the outer surface of the porous material is coated with a phase-separated mixture without any affect on the inner porosity;

Figure 8b shows a SEM micrograph of a coating applied to a porous poly(lactic-co-glycoloic acid [75:25] material that was included within the mold of Figure 8a prior to phase separation produced with the mixture formulation of 7% HEMA, 93% water, 0.05% APS, 0.04% SMBS, 4000 rpm (also listed in Table 1 as example 3).

Figure 9a shows a SEM micrograph of a cross-section of the wall of a cell-invasive, porous tube produced with the mixture formulation of 15.75% HEMA, 2.25% MMA, 82% water, 0.02% EDMA, 0.08% APS, 0.06% SMBS, 2700 rpm (also listed in Table 1 as example 4);

Figure 9b is an ESEM micrograph of a cross-section of the wall of a cell-invasive, porous tube produced with the mixture formulation of 20% HEMA, 80% water, 0.02% EDMA, 0.1 % APS, 0.04% TEMED, 2700 rpm (also listed in Table 1 as example 5);

Figure 10a shows an ESEM micrograph of a cross-section of the wall of a predominantly gel-like tube produced with the mixture formulation of 20% HEMA, 80% water, 0.02% EDMA, 0.1% APS, 0.06% SMBS, 10 000 rpm (also listed in Table 1 as example 6);

Figure 10b shows an ESEM micrograph of a cross-section of the wall of a predominantly gel-like tube produced with the mixture formulation of 23.25% HEMA, 1.75% MMA, 75% water, 0.025% EDMA, 0.125% APS, 0.1% SMBS, 2500 rpm (also listed in Table 1 as example 7);

Figure 11a shows an SEM micrograph of a cross-section of the wall of a mixed porous/gel-like tube produced with the mixture formulation of 28.3 % HEMA, 58.3 % water, 5.3% MMA, 8.3% ethylene glycol, 0.125% APS, 0.1% SMBS, 2700 rpm (also listed in Table 1 as example 8);

Figure 11b is a SEM micrograph of a cross-section of the wall of a mixed porous/gel-like tube, produced with the mixture formulation of 27% HEMA, 3% MMA, 70% water, 0.1% APS, 0.075% SMBS, 4000 rpm (also listed in Table 1 as example 9);

Figure 12a is an optical micrograph of a cross-section of the wall of a mixed porous/gel-like tube with radial pores made in a glass mold with the mixture formulation of 27% HEMA, 3% MMA, 70% water, 0.15% APS, 0.12% SMBS, 2700 rpm (also listed in Table 1 as example10);

Figure 12b shows an ESEM micrograph of a cross-section of the wall of a mixed porous/gel-like tube with radial pores made in a glass mold with the mixture formulation of 27% HEMA, 3% MMA, 70% water, 0.15% APS, 0.12% SMBS, 2700 rpm (also listed in Table 1 as example 10);

Figure 12c shows an optical micrograph of the outer longitudinal view of a mixed porous/gel-like tube with radial pores made in a glass mold with the mixture formulation of 27% HEMA, 3% MMA, 70% water, 0.15% APS, 0.12% SMBS, 2700 rpm (also listed in Table 1 as example 10);

Figure 12d shows an optical micrograph of the outer longitudinal view of a mixed porous/gel-like tube with no radial pores made in a silane-treated glass mold with the mixture formulation of 27% HEMA, 3% MMA, 70% water, 0.15%

APS, 0.12% SMBS, 2700 rpm (also listed in Table 1 as example 10). The hollow structure was synthesized with the same formulation as in 12(a-c), but spun in a silane-treated glass mold;

Figure 13a shows an ESEM micrograph of a cross-section of a predominantly gel-like wall with radial pores produced with the mixture formulation of 20% HEMA, 80% water, 0.1% APS, 0.04% SMBS, 2700 rpm (also listed in Table 1 as example 11);

Figure 13b shows a SEM micrograph of a cross-section of a predominantly porous wall with radial fibers produced with the mixture formulation of 2% HEMA, 98% water, 0.02% APS, 0.02% SMBS, 30 rpm (also listed in Table 1 as example 12);

Figure 14 shows a SEM micrograph of a cross-section of the wall of a multi-layered tube produced with the mixture formulation of (1st (outer) layer 1.8% HEMA, 0.2% PEGDMA, 98% water, 0.002% APS, 0.002% SMBS, 2700 rpm; 2nd (inner) layer 27% HEMA, 3% MMA, 70% water, 0.12% APS, 0.09% SMBS, 4000 rpm.) (also listed in Table 1 as example 13);

Figure 15 shows an ESEM micrograph of the inner lumen of a tube with a smooth inner surface produced with the mixture formulation of 20% HEMA, 80% water, 0.02% EDMA, 0.1% APS, 0.04% SMBS, 2700 rpm (also listed in Table 1 as example 14);

Figure 16a shows a SEM micrograph of the inner lumen of a tube with a rough inner surface produced with the mixture formulation of 28.3 % HEMA, 58.3 % water, 5.3% MMA, 8.3% ethylene glycol, 0.15% APS, 0.12% SMBS, 2700 rpm (also listed in Table 1 as example 15);

Figure 16b shows a SEM micrograph of a lateral cross-section of the wall of the tube shown in Figure 16a near the mold/polymer interface showing a gel-like/porous wall morphology and a dimpled/rough inner surface;

Figure 17a shows a SEM micrograph of a lateral cross-section of the wall of the tube near the mold/polymer interface showing a gel-like/porous wall morphology and a unique cell-like surface pattern on the inner surface produced with a formulation of 27.3% HEMA, 2.7%MMA, 70% water, 0.03%EDMA, 0.12% APS, 0.09% SMBS, 4000 rpm (also listed in Table 1 as example 16);

Figure 17b shows a SEM micrograph of cell-like surface patterns on the inner surface of a tube shown in Figure 17a;

Figure 18 shows a SEM micrograph of very small diameter micro-tubes manufactured with the mixture formulation of 22.5% HEMA, 2.5%MMA, 75% water, 0.125% APS, 0.1% SMBS, 4000 rpm (also listed in Table 1 as example 17), made in small diameter capillary tubing with an internal diameter of 450 μm ; and

Figure 19 is an optical micrograph of a non-uniformly shaped structure manufactured with the mixture formulation of 23.25% HEMA, 1.75%MMA, 75% water, 0.125% APS, 0.1% SMBS, 2500 rpm (also listed in Table 1 as example 17) wherein the mold size does not have a uniform internal diameter.

DETAILED DESCRIPTION OF THE INVENTION

[0022] The forces that generate the tubular structures in this novel process are inertial forces associated with spinning a mold. A mold is filled with a homogeneous solution containing at least two components that can be phase separated thereby displacing substantially all of the visible air inside the mold. The mold is then rotated at some pre-determined speed, for example by being inserted into a rotating device, such as a drill chuck, or lathe. Phase separation of this homogeneous solution is induced by a phase separating agent while the mold is spinning.

[0023] The spinning will only send one of the phases to the inner surface of the mold, therefore broadly speaking this phase which adopts the shape of the inner surface of the mold needs to be stabilized to produce the product. Specifically, this separated phase must be stabilized to prevent it from falling off the surface of the mold and returning to the solution and generally the method of stabilization will depend on the nature of the material in the separated phase.

[0024] When the products are polymeric, the components of the solution may contain monomers or polymers or both. The phase separation process may result from changes in solubility as induced by changes in polymer chain length, changes in temperature, creation of a chemical product within the mold, changes in pH, or exposure to light, electric or magnetic fields. The greater density of one of the phase-separated phases results in the phase adopting the shape of the inner surface of the mold.

[0025] Gelation of the separated phase fixes the morphology of the formed product and the solvent phase remains in the center of the mold. For certain types of materials, gelation of the deposited phase-separated phase can be achieved using a number of methods, including but not restricted to, continued polymerization in the separated phase (where the deposited phase comprise monomers), cooling or heating of the mold, creation of a chemical reaction product within the mold, changing the pH of the phase-separated mixture and shining a frequency of the ultra-violet/visible light at the phase-separated mixture. By controlling rotational speed, formulation chemistry, surface chemistry and dimensions of the mold, the resulting morphology, mechanical and porosity properties, of the resulting product can be manipulated.

[0026] Tubes made using the invention were synthesized in custom-built disposable molds, are shown in Figures 1a to 4c. Referring to Figure 1a, the mold, which may be a glass tubing A with an inside diameter (ID) between 0.02 and 100 mm, was cut to a desired length in the order of tens of centimeters. A septum B, currently made of rubber, was

slipped over each end of the glass tube to serve as an injection port. Referring to Figures 3a to 3c, the tubing A is filled using a needle D pushed through the upper injection port to permit the exit of air during liquid injection. The desired homogeneous liquid was injected via needle C through septum B at the lower end of the mold, displacing all of the air within the mold. Withdrawing the needles D, then C, results in a sealed, liquid filled mold. For concentricity and a uniform tube along the length, the sealed mold was placed into the chuck of a drill that had been mounted horizontally, using a spirit level.

[0027] Figures 1b, 1c and 1d show alternative embodiments of differently shaped molds that may be used to produce differently shaped tubes. For example, Figure 1d shows a mold with multiple variations in diameter along the length of the mold used to manufacture tubes with the same shape.

[0028] Figure 2a shows a cylindrical mold containing inner surface features such as rectangular fins on the inner surface used to manufacture tubes with rectangular indentations in the outer wall of the tubes. Figure 2b shows a cylindrical mold containing inner surface features such as convex spherical lumps on the inner surface used to manufacture tubes with concave spherical indentations in the outer wall. Figure 2c shows a cylindrical mold containing inner surface features such as pointed dimples on the inner surface used to manufacture tubes with dimples in the outer wall of the tube. Figure 2d shows a cylindrical mold containing inner surface features such as concave spherical lumps on the inner surface used to manufacture tubes with these features embedded in the wall of the resulting tubes. In all these embodiments the surface features can be of symmetrical or non-symmetrical order, and different surface features can be used in any combination.

[0029] The inner surface of the mold can be modified using a surface treatment, physical or chemical, that affects the morphology of the wall of the hollow structure. For example, as the separated phase can be liquid-like in nature, it can be induced to bead, and form droplets on the inner surface, thereby influencing the wall morphology. Similarly, the desired surface treatment can allow the separated phase to spread across the inner surface, also influencing the wall morphology.

[0030] Figures 4a, 4b and 4c show various schemes for rotation of the filled mold (A). In Figure 4a the mold A is inserted into a drill chuck (F) and rotation of mold is commenced. In Figure 4b the filled mold (A) is attached to the two ends of a lathe (G) and rotation of mold is commenced. In Figure 4c the filled mold (A) is inserted into an adapter (H) so it can be placed into a drill chuck (F) and rotation of mold is commenced. O-rings (I) maintain position of mold (A) inside the adapter (H).

[0031] Figures 5a and 5b show the process of phase separation during rotation of the mold. In Figure 5a the mold (A) filled with a homogeneous mixture (E) is rotated about an axis at a suitable speed to centrifuge the phase that will eventually separate. Figure 5b shows the mixture beginning to phase-separate during rotation. The dense phase (J) is centrifuged to the periphery of the mold where it adopts the shape of the mold (K).

[0032] It will be understood by those skilled in the art that the present method is not restricted to cylindrical molds or producing tubes therefrom. Any hollow structure may be used as a mold as long as it can be rotated about some axis to utilize centrifugal forces.

[0033] With the rotating mold containing the homogeneous liquid, phase separation of the mixture was induced, creating at least two phases from the liquid inside the mold. Phase separation may result in either liquid-liquid or viscoelastic solid-liquid interfaces or both within the mold. Phase separation can be induced using a range of different techniques and environmental changes. The addition of a propagating radical to a homogeneous monomer solution can induce phase separation, as can changes in temperature, pH, exposure of the mold to light, electric and magnetic fields.

[0034] After inducing different phases within the homogeneous solution, one or more of the phases will be forced to the periphery if the densities of the phases are different. The phase-separated particles then gel together, through covalent or physical bonding, to form a three-dimensional network between the separated phase(s). The gelation of particles must commence at a finite time after the onset of phase separation within the process of the invention.

[0035] A porous material can have an outer coating applied to it using this technology. Prior to the injection of a homogeneous mixture into the mold, a plug of porous material is inserted into the mold (Figure 8a). After insertion of the porous structure into the mold, a homogeneous mixture is injected into the mold and rotated at the desired speed. The phase-separated phase is centrifuged through the pores of the inserted plug, and forms a structure on the outer surface of the porous plug, therefore sealing the material, without blocking the internal pores.

[0036] In a preferred embodiment of the present invention the homogenous solution includes at least two or more phases, one being a monomer, or polymer, and the other a solvent.

[0037] For homogeneous solutions containing monomer to be initiated, the initiation agent may be free radical initiators, thermal initiators and redox initiators. Examples of initiators includes ammonium persulfate or potassium persulfate with sodium metabisulfite, or tetramethylethylene diamine or ascorbic acid, azonitriles and derivatives thereof, alkyl peroxides and derivatives thereof, acyl peroxides and derivatives thereof, hydroperoxides and derivatives thereof; ketone peroxides and derivatives thereof, peresters and derivatives thereof and peroxy carbonates and derivatives thereof.

[0038] The homogeneous solution could also include a cross-linking agent depending on the structure of the final product that is desired and the polymer material that is formed. The crosslinking agent may be a multifunctional molecule

with at least two reactive functionalities and includes multi-functional methacrylates or multi-functional acrylates, multi-functional acrylamides or multi-funtional methacrylamides, or multi-functional star polymers of polyethylene glycol and preferably, but not limited to, one of ethylene glycol dimethacrylate (EDMA), hexamethylene dimethacrylate (HDMA), poly(ethylene glycol) dimethacrylate, 1,5-hexadiene-3,4-diol (DVG), 2,3-dihydroxybutanediol 1,4-dimethacrylate (BHD-MA), 1,4-butanediol dimethacrylate (BDMA), 1,5-hexadiene (HD), methylene bisacrylamide (MBAm) multi-functional star polymers of poly(ethylene oxide) or combinations thereof.

[0039] An exemplary, non-limiting list of monomers that may be in the homogeneous mixture includes any one of acrylates, methacrylates, and derivatives thereof such as, but not limited to, 2-hydroxyethyl methacrylate, methyl methacrylate, 2-polyethylene glycol ethyl methacrylate, ethyl acrylate, 2-hydroxyethyl acrylate, acrylic acid, methacrylic acid, 2-chloroethyl methacrylate, butyl methacrylate, glycidyl methacrylate, hydroxypropyl methacrylate; acrylamides and derivatives thereof such as, but not limited to, methacrylamide, hydroxypropyl methacrylamide, N,N-diethyl acrylamide, N,N-dimethyl acrylamide, 2-chloroethyl acrylamide, 2-nitrobutyl acrylamide, ; N-vinyl pyrrolidone, acenaphthalene, N-vinyl acetamide, phenyl-acetylene, acrolein, methyl acrolein, N-vinyl pyridine, vinyl acetate, vinyl chloride, vinyl fluoride, vinyl methyl ketone, vinylidene chloride, styrene and derivatives thereof, propene, acrylonitrile, methacrylonitrile, acryloyl chloride, allyl acetate, allyl chloride, allylbenzene, butadiene and derivatives thereof, N-vinyl caprolactam, N-vinyl carbazole, cinnamates and derivatives thereof, citraconimide and derivatives thereof, crotonic acid, diallyl phthalate, ethylene and derivatives thereof such as, but not limited to 1,1 diphenyl-ethylene, chlorotrifluoro-ethylene, dichloroethylene, tetrachloro-ethylene; fumarates and derivatives thereof, hexene and derivatives thereof, isoprene and derivatives thereof such as, but not limited to isopropenyl acetate, isopropenyl methyl ketone, isopropenylisocyanate; itaconate and derivatives thereof; itaconamide and derivatives thereof; diethyl maleate, 2-(acryloyloxy)ethyl diethyl phosphate, vinyl phosphonates and derivatives thereof, maleic anhydride, maleimide, silicone polymers, and derivatives thereof; and any combination thereof.

[0040] An exemplary, non-limiting list of polymers that may be in the homogeneous mixture includes any of polyacrylates, polysulfone, peptide sequences, proteins, oligopeptides, collagen, fibronectin, laminin, polymethacrylates such as but not limited to poly(methyl methacrylate), poly(ethoxyethyl methacrylate), poly(hydroxyethylmethacrylate; polyvinyl acetates polyacetates, polyesters, polyamides, polycarbonates, polyanhydrides, polyamino acids, such as but not limited to poly(N-vinyl pyrrolidinone), poly(vinyl actetate), poly(vinyl alcohol, poly(hydroxypropyl methacrylamide), poly(caprolactone), poly(dioxanone) polyglycolic acid, polylactic acid, copolymers of lactic and glycolic acids, and polytrimethylene carbonates, poly(butadiene), polystyrene, polyacrylonitrile, poly(chloroprene), neoprene, poly(isobutene), poly(isoprene), polypropylene, polytetrafluoroethylene, poly(vinylidene fluoride), poly(chlorotrifluoroethylene), poly(vinyl chloride), poly(oxymethylene), poly(ethylene terephthalate), poly(oxyethylene) poly(oxyterephthaloyl), polyamides such as but not limited to, poly[imino(1-oxohexamethylene)], poly(iminoadipoyl-iminohexamethalene), poly(iminohexamethylene-iminosebacoyl), poly[imino(1-oxododecamethylene)], cellulose, polysulfones, hyalonic acid, sodium hyaluronate, alginate, agarose, chitosan, chitin, and mixtures thereof.

[0041] A non-limiting exemplary list of solvents in the homogeneous mixture for the monomer and/or polymers includes any neucleophilic or electrophilic molecule including, but not necessarily restricted to water, alcohols, ethylene glycol, ethanol, acetone, poly(ethylene glycol), dimethyl sulfoxide, dimethyl formamide, alkanes and derivatives thereof, acetonitrile, acetic acid, benzene, acetic anhydride, benzyl acetate, carbon tetrachloride, chlorobenzene, n-butanol, 2-chloroethanol, chloroform, cyclohexane, cyclohexanol, dichloromethane, diethyl ether, di(ethylene glycol), di(ethylene glycol) monomethyl ether, 1,4 dioxane, N,N, dimethyl acetamide, N,N, dimethyl formamide, ethyl acetate, formaldehyde, n-heptane, hexachloroethane, hexane, isobutanol, isopropanol, methanol, methyl ethyl ketone, nitrobenzene, n-octane, n-pentanol, propyl acetate, propylene glycol, pyridene, tetrahydrofuran, toluene, trichloroethylene, o-xylene and p-xylene, or aforementioned monomers or crosslinking agents, or mixtures thereof.

[0042] The solvent can be chosen to solubilize the monomer but not a polymer or crosslinked polymer formed from the monomer. One of the components may include a polymer dissolved in a solvent.

[0043] In another embodiment a tapered hollow structure with changing dimensions along it length can be manufactured where the sealed mold is rotated at a predetermined angle between 0 and 90° from the horizontal plane.

[0044] In another embodiment controlling the viscoelastic properties of the separated phase and/or the rotation speed can create cell-invasive hollow structures. If the separated phase has substantial elastic properties, they will not coalesce, and after gelation, the porous network between the phase is large enough for the penetration of cells into the construct.

[0045] In another embodiment multi-layered structures can be formed by repeating the process as many times as desired. After forming the first layer, the solvent phase can be removed and another homogeneous mixture injected into the mold. The first layer coating the mold, effectively becomes the mold for the next coating and the second formation penetrates into the first coating, binding them together after gelation. The multi-layered hollow structures can be manufactured using any or all of the types of tubes described in the examples, made from any material, similar or different materials, in any order required, as many times as required. A layered wall structure (ie. gel-like and porous) can be made by multiple formulations and multiple rotations or in one formulation/one rotation.

[0046] Manufacture of both physically and chemically crosslinked tubes are possible using this technique, as is the

manufacture of both degradable and nondegradable polymer tubes. Those skilled in the art will appreciate the many applications for which the structures produced with the present method may be used. The ability to control the morphology, porosity and wall thickness of these tubes permits their use as drug delivery vehicles, when the structures are composed of physiologically acceptable materials. Drugs can also be incorporated in other materials that are incorporated into the tube, or in the tube wall itself. For example, the tube can be filled with a material, such as, but not limited to, a hydrogel, in which drugs are dispersed. Alternatively, the wall structure can serve as a reservoir for the drug, which may be incorporated in another material/drug reservoir, such as microspheres releasing the drug. The drug may be delivered uniformly or in a gradient. By tuning the set-up, a gradient can be established. The drug may include, but is not limited to, proteins, peptides, genes, vectors, growth factors, hormones, oligonucleotides, cell products, or cells or combinations thereof.

[0047] It is also possible to produce hollow structures that allow molecules to diffuse across the wall structure. Also hollow structures can be produced that selectively allow the diffusion of molecules based on size and/or shape to diffuse across the wall structure and to allow preferential directional drug delivery. The invention can also provide tubular structures with the appropriate mechanical properties for their end use - for example to match the mechanical properties of the tissue in which they are to be implanted.

[0048] The present method can be used to produce tubular structures that have an outer gel phase and an inner porous phase. The present method can also be used to provide a tubular structure with overlapping regions of porous phase/gel phase.

[0049] A significant advantage of the present method can be used to make hollow structures of various dimensions with internal diameters from 10μm to 100cm.

[0050] The present invention will now be illustrated with several non-limiting examples. The first examples relate to 2-hydroxyethyl methacrylate polymers and copolymers that are synthesized (and crosslinked) in a rotating mold where phase separation precedes gelation of polymer networks formed, resulting in a tube due to centrifugal forces. Such morphologies given as examples of 2-hydroxyethyl methacrylate and its copolymers are also relevant to any monomeric or polymeric system that can be induced to phase separate in a liquid-filled rotating mold.

Example 1

[0051] 2-hydroxyethyl methacrylate (HEMA) was polymerized in the presence of excess water, with a crosslinking agent, preferably, but not limited to ethylene dimethacrylate (EDMA), using a free radical initiating system and preferably an ammonium persulfate (APS)/sodium metabisulfite (SMBS) redox initiating system. A homogeneous mixture, with components detailed in Table 1, was injected into a cylindrical glass mold as described for the process involving 2-hydroxyethyl methacrylate. The homogeneous mixture was made by adding the relevant quantities of HEMA, and water into a glass vial, and mixing in the glass vial. Mixing of the solution was repeated after the appropriate amount of 10% APS solution listed in Table 1 was added. The appropriate volume of 10% SMBS solution was added to this mixture, which was mixed for an additional 30 seconds. The homogeneous monomer mixture was then drawn into a Luer-lok syringe using a 20-gauge needle. The needle was removed from the syringe and, using a new 20-gauge needle and a 0.8 μm filter, the monomer mixture was injected into the polymerization molds.

[0052] The sealed mold was placed in the chuck of a RZR-1 dual range, variable speed stirring drill (Heidolph, Germany) that had been mounted horizontally, using a spirit level. The rotational speed was 2700 rpm as listed in Table 1. The resulting gel-like coating on the inner surface of the mold is shown in Figure 6 and is approximately 10±3 μm thick. Figure 6 shows an environmental scanning electron microscope (ESEM) micrograph of a gel-like coating on the inside of a glass mold, in which the mixture formulation was 1% HEMA, 99% water, 0.01 %APS, 0.01% SMBS, 4000 rpm.

Example 2

[0053] A coating with both gel-like and porous morphologies was prepared with the same methodology as Example 1; the monomer mixture used also included poly(ethylene glycol) methacrylate as a comonomer. The monomer mixture and rotation.conditions used in Example 2 are listed in Table 1. The resulting porous materiallgel-like hybrid coating on the inner surface of the mold is shown in Figures 7a and 7b with the outer gel-like coating (the surface that is against the inside of the mold) facing forward in Figure 7a and the inner porous structure (the one against the water) facing forward in Figure 7b. The thickness of the coating is approximately 30±5 μm thick. The micrograph in Figures 7a and 7b were taken after removing the coating from the glass mold. More specifically, Figure 7a shows a scanning electron microscope (SEM) micrograph of the outer surface of a porous coating applied to the inside of a glass mold, in which the mixture is 1.9% HEMA, 0.1% PEGMA, 98% water, 0.02% APS, 0.02% SMBS, 2700 rpm. Figure 7b shows the inner surface of a porous coating applied to the inside of a glass mold, in which the mixture formulation is 1.9% HEMA, 0.1 % PEGMA, 98% water, 0.02% APS, 0.02% SMBS, 2700 rpm.

Example 3

[0054] A porous material can have an outer coating applied to it using this technology. The coating that can be either gel-like or have porous morphology or both was prepared with similar methodology as in Example 1. Prior to the injection of a homogeneous mixture into the mold, a plug of porous material is inserted into the mold (Figure 8a). Porous PLGA is manufactured using techniques previously described (Holy et al, Biomaterials, 20, 1177-1185, 1999), however the porous material may be made of any material, including polymers, ceramics, metals; composites, or combinations thereof. After insertion of the porous structure into the mold, the homogeneous mixture listed in Table 1 as Example 3 is injected into the mold and the mold rotated at the speed listed in Table 1. The resulting coated porous material removed from the mold is shown in Figure 8b. There was no coating or blocked pores on the inside of the porous material; the only coating visible was on the outside. This example demonstrates the successful outer coating (and sealing) of a porous material without affecting the morphology of the said porous material.

Example 4-5

[0055] A porous, cell-invasive tube can be manufactured with the same methodology as Example 1, except the monomer mixture used may include methyl methacrylate (MMA) as a comonomer. Example 5 also substitutes TEMED for SMBS as the second component in the initiating system. The monomer mixture and rotation conditions used in Examples 4-5 are listed in Table 1, and both result in cell invasive, porous tubes. In this particular instance, the use of a faster initiating system, such as, but not limited to the APS/TEMED redox system, or increased concentrations of initiator in the homogeneous mixture is beneficial to achieve the porous structure. Figures 9a and 9b show a porous wall morphology of Examples 4 and 5. Formation is due to sudden phase separation, in addition to viscoelastic particles separating, that do not coalesce.

Examples 6-7

[0056] A semi-porous, cell-impermeable tube can be manufactured with the same methodology as Example 1, except the monomer mixture used may include methyl methacrylate (MMA) as a comonomer. The monomer mixture and rotation conditions used in Examples 6-7 are listed in Table 1, and both result in semipermeable non-cell invasive, tubes. In example 6, the rotation speed is at 10,000 rpm; the high rotation speed compacts the phase separating structure against the tube wall, resulting in gel-like wall morphology with closed cell pores that affect diffusion across the wall membrane (Figure 10a).

[0057] In the instance of example 7, the initiating system as a phase separating agent may be in a lower concentration, as slower phase separation is beneficial to achieve the non-porous, gel-like structure at lower rotation speeds (Figure 10b).

Examples 8-9

[0058] A mixed porous/gel-like tube can be manufactured with the same methodology as Example 1, except the monomer mixture used may include MMA and/or ethylene glycol EG) which affects phase separation. The monomer mixture and rotation conditions used in Examples 8-9 are listed in Table 1, and both result in mixed porous and gel-like tubes manufactured with one polymerization. The bi-layer morphology of the cross-section of Example 8, seen in Figure 11a, is due to the precipitation of a liquid-like phase at the start of the phase separation followed by a viscoelastic precipitate towards the end of the phase separation. Co-solvents other than water, such as EG, are therefore useful for delaying or accelerating phase separation, and therefore control the bilayered morphology of the wall.

[0059] For Example 9, a porous/gel-like tube can be manufactured with the same methodology as Example 1, except faster speeds in combination with slower phase separation can induce the morphology in Figure 11b.

Example 10

[0060] A mixed porous/gel-like tube with radial porosity can be manufactured with the same methodology as Example 1, when the denser separating phase can be beaded as droplets on the inner surface of the rigid mold. The contact angle of the separating phase can be influenced by surface modification of the rigid mold, or changing the material of the inside of the mold. The wall morphology can therefore be influenced by the surface chemistry of the mold. The monomer mixture and rotation conditions used in Example 10 are listed in Table 1, may include co-solvents such as methyl methacrylate or ethylene glycol to influence the solubility of the separated phase. Figures 12a and 12b are micrographs of the porous/gel-like tube with radial porosity cross-section, with Figure 12c showing the outer longitudinal morphology of the same formulation. The hollow structure shown in the optical micrograph in Figure 12d was synthesized with the same formulation as Example 10, but was formed in a silane-treated glass mold. The silanating agent was

Sigmacote from Sigma-Aldrich. The Sigmacote solution was drawn up into glass molds and then dried in an oven to evaporate the solvent. Contact angle studies on glass slides showed the water contact angle changed from $44.7\pm3°/11.6\pm1.8°$ to $47\pm0.3°/44\pm0.4°$ after surface modification. The glass mold was then used with the formulation listed as Example 10 in Table 1. The hollow fiber membranes had equilibrium water contents between 42% and 57%; elastic moduli between 22 kPa and 400 kPa, and diffusive permeabilities between 10^{-7} and 10^{-9} cm^2s^{-1} for vitamin B12 and dextran 10kD. Similar mechanical strengths of the tube walls could be achieved with significantly different permeabilities, reflecting their intrinsic microstructures. The beading described in Example 10 permits highly diffusive hollow structures while maintaining good mechanical strength.

Example 11

[0061] A porous tube with pores that are radial in nature can be manufactured with the same methodology as Example 1, with a monomer formulation mixture and rotation conditions listed in Table 1 as Example 11. The wall morphology is predominantly gel, with channels or pores that penetrate in a radial manner that does not require beading as in Example 10. An example of this morphology is shown in Figure 13a.

Example 12

[0062] A porous tube with fibers that are radial can be manufactured with the same methodology as Example 1, with a monomer formulation mixture and rotation conditions listed in Table 1 for Example 12. The wall morphology is predominantly space, with fibers that penetrate in a radial manner. The inner lumen of the formed hollow structure is small relative to the wall thickness and an example of this morphology is shown in Figure 13b. In this example, the prevention of sedimentation of low concentrations was achieved with a slow rotation rate. This surprising result demonstrates the profound effect of rotation rate on the wall morphology, especially compared to Example 2 (Figure7a and 7b) which has the similar monomer concentrations, but significantly different rotation rates.

Example 13

[0063] Morphology of a cross-section of the wall of a multi-layered tube with the mixture formulation listed in Table 1 as example 13. These multi-layered tubes are can be manufactured with the same methodology as Example 1, repeated as many times as required. Example 13 in Table 1 refers to the first, outer, layer formed (o) and the second, inner formed layer (i). Multi-layered hollow structures are possible by forming one layer and using the formed hollow structure as the surface coating of the mold and the hollow structure process repeated as many times as desired. The multi-layered hollow structures can be manufactured using any or all of the types of tubes described in the examples, made from any material, similar or different materials, in any order required, as many times as required. An example is shown in Figure 14.

Example 14

[0064] Smooth surface morphology the inner layer of a tube with the mixture formulation listed in Table 1 as Example 14 can be manufactured with the same methodology as Example 1. A tube with a smooth inner surface is shown in Figure 15.

Example 15

[0065] Dimpled/rough surface morphology on the inner layer of a tube, which can be made using the mixture formulation listed in Table 1 as example 15, can be manufactured with the same methodology as Example 1. A tube with a dimpled/rough inner surface is shown in Figure 16a. A lateral cross-section of the tube showing a gel-like/porous wall morphology and a dimpled/rough inner surface is shown in Figure 16b.

Example 16

[0066] Unique surface morphology of the inner lumen of a tube with unique cell-like surface patterns can be made using the mixture formulation listed in Table 1 as example 16 manufactured with the same methodology as Example 1. Surface morphologies such as those seen in Figure 17a are created using this process. Figure 17b shows such cell-like surface patterns on the inner lumen of a tube with a gel-like/porous wall morphology.

Example 17

[0067] Very small diameter micro-tubes can be manufactured with the same methodology as Example 1, except the mold size is very narrow. Figure 18 is a tube that was manufactured from a mixture formulation listed in Table 1 as example 17 in small diameter capillary tubing with an internal diameter of 450 μm. Smaller tubing can be created by using molds with an internal diameter of 10μm and larger.

Example 18

[0068] Various shaped structures can be manufactured with the same methodology as Example 1, except the mold size is neither cylindrical nor has a uniform internal diameter. Figure 19 is a tube that was manufactured from a mixture formulation listed in Table 1 as example 18, in a mold with a variable diameter. Any example formulation can be used to create this shape of hollow structure.

Example 19

[0069] A tapered hollow structure with changing dimensions along it length can be manufactured with the same methodology as example 1, except the sealed mold was placed into the chuck of a drill that had been mounted at a predetermined angle between 0 and 90° from the horizontal plane.

Example 20

[0070] A hollow structure with variable wall thickness or holes along the length can be manufactured with the same methodology as example 1, except the sealed mold has some inner surface morphologies, such as in Figure 2a-d. Any example formulation can be used to create this shape of hollow structure.

Example 21

[0071] Hollow structures can be manufactured from the liquid-liquid phase separation of a polymer solution using temperature as the phase separating agent. Poly(lactic-co-glycolic acid) was dissolved in a 87:13 (wt%) dioxane/water mixture at 60°C to create a solution that is injected into pre-heated glass molds. After injecting in a sealed glass mold, removing all air from the mold, it was placed in the chuck of a drill at room temperature and spun at 4000 rpm. The mold was allowed to cool to room temperature, which induced liquid-liquid phase separation and gelation. The mold was then frozen and the dioxane/water mixture removed by placing in a freeze-dryer. The formed tube is then removed from the mold.

Example 22

[0072] N-2-(hydroxypropyl) methacrylamide (HPMA) (30 vol%) was polymerized in the presence of excess acetone/ dimethyl sulfoxide (DMSO) (93:7 v/v), with a crosslinking agent, preferably, but not limited to methylene bisacrylamide (1 mol%), using azobisisobutyronitrile (AIBN) as an initiating system. A monomeric sugar may or may not be also added to the polymerization mixture. The mixture was fully mixed, and injected into a cylindrical glass mold as described for Example 1 using the mixture formulation listed in Table 1 as example 22.

[0073] The sealed mold was placed in the chuck of a stirring drill that had been mounted horizontally, using a spirit level and rotated at 4000 rpm at 50°C for 24 hours. The resulting hollow structure on the inner surface of the mold is removed from the mold.

[0074] The foregoing description of the preferred embodiments of the invention has been presented to illustrate the principles of the invention and not to limit the invention to the particular embodiment illustrated. It is intended that the scope of the invention be defined by all of the embodiments encompassed within the following claims.

Table 1. Example Fmulations

Example #	Monomer 1	Monomer 2	Monomer 3	Solvent 1	Solvent 2	Initiator 1	Accelerator	Rotation	Tube ID
1	1% HEMA			99% water		0.01% APS	0.01% SMBS	4000 rpm	2.4 mm
2	1.9% HEMA	0.1 % PEGMA		98% water		0.02% APS	0.02% SMBS	2700 rpm	3.2 mm
3	7% HEMA			93% water		0.05% APS	0.04% SMBS	4000 rpm	7.5 mm
4	15.75% HEMA	2.25% MMA	0.02% EDMA	82% water		0.08% APS	0.06% SMBS	2700 rpm	3.2 mm
5	20% HEMA	0.06% EDMA		80% water		0.1% APS	0.04% TEMED	2700 rpm	2.4 mm
6	20% HEMA		0.02% EDMA	80% water		0.1% APS	0.06% SMBS	10000 rpm	2.4 mm
7	23.25% HEMA	1.75% MMA		75% water		0.125% APS	0.1% SMBS	2500 rpm	3.2 mm
8	28.3% HEMA	5.3% MMA		58.3% water	8.3% EG	0.125%APS	0.1% SMBS	2700 rpm	1.8 mm
9	27% HEMA	3% MMA		70% water		0.1 APS	0.075% SMBS	4000 rpm	2.4 mm
10	27% HEMA	3% MMA		70% water		0.15% APS	0.12% SMBS	2700 rpm	2.4 mm
11	20% HEMA			80% water		0.1% APS	0.4% SMBS	2700 rpm	3.2 mm
12	2% HEMA			98% water		0.02% APS	0.02% SMBS	30 rpm	3.2 mm
13 (o) 13 (i)	1.8%HEMA 27% HEMA	0.2% PEGMA	 3% MMA	98% water 70% water		0.002% APS 0.12% APS	0.002%SMBS 0.09% SMBS	2700 rpm 4000 rpm	3.2 mm
14	20% HEMA		0.02% EDMA	80% water		0.1% APS	0.04% SMBS	2700 rpm	2.4 mm
15	28.3% HEMA	5.3% MMA		58.3% water	8.3% EG	0.15%APS	0.12% SMBS	2700 rpm	1.8 mm
16	27.3% HEMA	2.7% MMA	0.03% EDMA	70% water		0.12% APS	0.09% SMBS	4000 rpm	3.2 mm
17	22.5% HEMA	2.5% MMA		75% water		0.125% APS	0.1% SMBS	4000 rpm	0.45 mm
18	23.25% HEMA	1.75% MMA		75% water		0.125% APS	0.1% SMBS	2500 rpm	2.8 mm to 5.8 mm
22	30 vol% HPMA	1% MBAm		65% acetone	4.9% DMSO	1% AIBN		4000 rpm	3.2 mm

Claims

1. A process of producing a product, comprising :

   a) filling an interior of a mold (A) with a solution (E) so that substantially all air is displaced therefrom, the solution (E) comprising at least two components which can be phase separated by a phase separation agent into at least two phases;
   b) rotating said mold (A) containing said solution (E) at an effective rotational velocity in the presence of said phase separation agent to induce phase separation between said at least two components into at least two phases so that under rotation at least one of the phases (J) deposits onto an inner surface (K) of the mold (A); and
   c) forming said product by stabilizing said at least one of the phases (J) deposited onto the inner surface (K) of the mold (A).

2. The process according to claim 1 including removing said product from said mold.

3. The process according to claims 1 or 2 wherein said at least two components includes at least one monomer and at least one solvent, and wherein said solution is a substantially homogenous solution, wherein said at least one of the phases that deposits onto the inner surface includes at least the monomer, and wherein the step of stabilizing said deposited phase includes gelation of the monomer by polymerization thereof.

4. The process according to claim 3 wherein said phase separation agent is selected from the group consisting of light, pH, initiation agents, change in temperature, creation of a chemical product within the mold, changes in cationic and/or anionic concentrations, electric and magnetic fields.

5. The process according to claim 4 wherein said initiation agent is selected from the group consisting of free radical initiators, thermal and photo initiators and redox initiators.

6. The process according to claims 1 or 2 wherein said at least two components includes at least one polymer dissolved in at least one solvent, and wherein said solution is a substantially homogenous solution, wherein said at least one of the phases that deposits on the inner surface includes at least the polymer, and wherein the step of stabilizing said deposited phase includes gelation thereof.

7. The process according to claim 6 wherein said phase separation agent is selected from the group consisting of light, change in pH, change in temperature, creation of a chemical product within the mold, changes in cationic and/or anionic concentrations, electric and magnetic fields.

8. The process according to claim 6 wherein gelation is achieved by exposure to an agent selected from the group consisting of light, change in pH, change in temperature, creation of a chemical product within the mold, changes in cationic and/or anionic concentrations, electric and magnetic fields.

9. The process according to claims 3 or 6 wherein said hollow mold is a cylindrical tube so that said product is a polymeric tube.

10. The process according to claim 9 wherein said cylindrical tube includes preselected surface features on said inner surface of the cylindrical tube.

11. The process according to claims 1 or 2 including inserting a porous structure into said mold prior to filling said mold with said solution, and wherein said product is coated on an outer surface of said porous structure.

12. The process according to claims 3 or 6 wherein said solution includes a cross-linking agent.

13. The process according to claim 12 wherein the crosslinking agent is selected from the group consisting of multifunctional methacrylate, acrylate, acrylamide, methacrylamide, 1,5-hexadiene-3,4-diol, 1,5-hexadiene (HD) multifunctional star polymers of poly(ethylene oxide).

14. The process according to claim 3 wherein said monomer is selected from the group consisting of acrylates, methacrylates, acrylic acid, methacrylic acid, acrylamide, methacrylamide and derivatives thereof; N-vinyl pyrrolidone, acenaphthalene, N-vinyl acetamide, phenyl-acetylene, acrolein, methyl acrolein, N-vinyl pyridine, vinyl acetate, vinyl

chloride, vinyl fluoride, vinyl methyl ketone, vinylidene chloride, styrene and derivatives thereof, propene, acrylonitrile, methacrylonitrile, acryloyl chloride, allyl acetate, allyl chloride, altylbenzene, butadiene and derivatives thereof, N-vinyl caprolactam, N-vinyl carbazole, cinnamates and derivatives thereof, citraconimide and derivatives thereof, crotonic acid, diallyl phthalate, ethylene and derivatives thereof; fumarates and derivatives thereof, hexene and derivatives thereof, isoprene and derivatives thereof; itaconate and derivatives thereof; itaconamide and derivatives thereof; diethyl maleate, 2-(acryloyloxy)ethyl diethyl phosphate, vinyl phosphonates and derivatives thereof, maleic anhydride, maleimide, silicone monomers, and derivatives thereof; and any combination thereof.

15. The process according to claim 3 or 6 wherein said solvent is selected from the group consisting of nucleophilic or electrophilic molecules selected from the group consisting of water, alcohols, ethylene glycol, ethanol, acetone, poly (ethylene glycol), dimethyl sulfoxide, dimethyl formamide, alkanes and derivatives thereof, acetonitrile, acetic acid, benzene, acetic anhydride, benzyl acetate, carbon tetrachloride, chlorobenzene, n-butanol, 2-chloroethanol, chloroform, cyclohexans, cyclohexanol, dichloromethane, diethyl ether, di(ethylene glycol), di(ethylene glycol) monomethyl ether, 1,4-dioxane, N,N'-dimethyl acetamide, N,N'-dimethyl formamide, ethyl acetate, formaldehyde, n-heptane, hexachloroethane, hexane, isobutanol, isopropanol, methanol, methyl ethyl ketone, nitrobenzene, n-octane, n-pentanol, propyl acetate, propylene glycol, pyridine, tetrahydrofuran, toluene, trichloroethylene, o-xylene and p-xylene, a monomer, a liquid crosslinking agent, or mixtures thereof.

16. The process according to claims 3 wherein said solvent solubilizes said monomer but not a polymer or crosslinked polymer formed from said monomer.

17. The process according to claims 3 wherein said at least one monomer is present in a range from about 0.001 % by weight to about 60% by weight.

18. The process according to claim 6 wherein said polymer is selected from the group consisting of polyacrylates, polysulfones, peptide sequences, proteins, oligopeptides, collagen, fibronectin, laminin, polymethacrylates, polyacetates, polyesters, polyamides, polycarbonates, polyanhydrides, polyamino acids, cellulose, hyaluronic acid, sodium hyaluronate, alginate, agarose, chitosan, chitin, and mixtures thereof.

19. The process according to claim 1 including physically or chemically modifying the inner surface of the mold upon which preselected morphologies are induced into the wall of the said product by inducing beading or spreading of the separated liquid phase.

20. The process according to claim 19 with molecules including silanating agents.

21. The process according to claims 3 or 6 including the step of removing the solvent and including repeating steps a), b) and c), at least once to produce a multi-layered product.

22. The process according to claim 19 wherein the preselected wall morphologies are selected from a group consisting of a porous structure, a gel structure and overlapping regions of porous/gel structure.

23. The process according to claim 19 wherein the preselected wall morphologies comprise a predominantly gel morphology with porous channels running from a periphery to a lumenal side, resulting in spotting on an outer wall surface.

24. The process according to claim 19 wherein the wall structure is used as a reservoir for the delivery of drugs, therapeutics, cells, cell products, genes, viral vectors, proteins, peptides, hormones, carbohydrates, growth factors.

25. The process according to claim 1 wherein the solution contains microspheres containing preselected constituents, and wherein the product includes said microspheres distributed either uniformly or in a gradient within the wall structure of the product.

26. The process according to claim 12 wherein the crosslinking agent is selected from the group consisting of ethylene glycol dimethacrylate (EDMA), hexamethylene dimethacrylate (HDMA), poly(ethylene glycol) dimethacrylate, 2.3-dihydroxybutanediol 1,4-dimethacrylate (BHDMA) and 1,4-butanediol dimethacrylate (BDMA).

27. The process according to claim 3 wherein said monomer is selected from the group consisting of 2-hydroxyethyl methacrylate, methyl methacrylate, 2-polyethylene glycol ethyl methacrylate, ethyl acrylate, 2-hydroxyethyl acrylate, 2-chloroethyl methacrylate, butyl methacrylate, glycidyl methacrylate, hydroxypropyl methacrylate; hydroxypropyl

methacrylamide, N,N-diethyl acrylamide, N,N-dimethyl acrylamide, 2-chloroethyl acrylamide, 2-nitrobutyl acrylamide; 1,1 diphenyl-ethylene, chlorotrifluoro-ethylene, dichlaroethylens, tetrachloro-ethylene; isopropenyl acetate, isopropenyl methyl ketone, isopropenylisocyanate; and any combination thereof.

28. The process according to claim 6 wherein said polymer is selected from the group consisting of poly(methyl methacrylate), poly(ethoxyethyl methacrylate), poly(hydroxyethylmethacrylate); poly(N-vinyl pyrrolidinone), polyvinyl acetate, polyvinyl alcohol, poly(hydroxypropyl methacrylamide), poly(caprolactone), poly(dioxanone) polyglycolic acid, polylactic acid, copolymers of lactic and glycolic acids, and polytrimethylene carbonates, poly(butadiene), polystyrene, polyacrylonitrite, poly(chloroprene), neoprene, poly(isobutene), poly(isoprene), polypropylene, polytetrafluoroethylene, poly(vinylidene fluoride), poly(chlorotrifluoroethylene), poly(vinyl chloride), poly(oxymethylene), poly(ethylene terephthalate), poly(oxyethylene) poly(oxyterephthaloyl); poly[imino(1-oxohexamethylene)], poly(iminoadipoyliminohexamethalene), poly(iminohexamethylene-iminosebacoyl), poly[imino(1-oxododecamethylene)], and mixtures thereof.

Patentansprüche

1. Verfahren für das Herstellen eines Produkts, umfassend:

   a) das Füllen eines Innenraums einer Form (A) mit einer Lösung (E) derart, dass im Wesentlichen die gesamte Luft daraus verdrängt wird, wobei die Lösung (E) mindestens zwei Komponenten umfasst, die durch ein Phasentrennungsmittel in mindestens zwei Phasen phasengetrennt werden können;
   b) das Rotieren der Form (A), die die Lösung (E) enthält, mit einer wirksamen Rotationsgeschwindigkeit in Gegenwart des Phasentrennungsmittels, um die Phasentrennung zwischen den mindestens zwei Komponenten in mindestens zwei Phasen auszulösen, derart, dass unter Rotation mindestens eine der Phasen (J) sich auf einer Innenfläche (K) der Form (A) absetzt und
   c) das Bilden des Produkts durch Stabilisieren mindestens einer der Phasen (J), die auf der Innenfläche (K) der Form (A) abgesetzt worden ist.

2. Verfahren nach Anspruch 1 umfassend das Entfernen des Produkts von der Form.

3. Verfahren nach Anspruch 1 oder 2, wobei die mindestens zwei Komponenten mindestens ein Monomer und mindestens ein Lösungsmittel umfassen und wobei die Lösung eine im Wesentlichen homogene Lösung ist, wobei mindestens eine der Phasen, die auf der Innenfläche abgesetzt werden, mindestens das Monomer umfasst und wobei der Schritt des Stabilisierens der abgesetzten Phase die Gelbildung des Monomers durch Polymerisation desselben umfasst.

4. Verfahren nach Anspruch 3, wobei das Phasentrennungsmittel aus der Gruppe ausgewählt ist bestehend aus Licht, pH-Wert, Initiatoren, Änderung der Temperatur, Bildung eines chemischen Produkts innerhalb der Form, Änderungen der kationischen und/oder anionischen Konzentrationen, elektrischen und magnetischen Feldern.

5. Verfahren nach Anspruch 4, wobei der Initiator aus der Gruppe ausgewählt ist bestehend aus Radikalinitiatoren, Wärme- und Fotoinitiatoren und Redoxinitiatoren.

6. Verfahren nach Anspruch 1 oder 2, wobei mindestens zwei Komponenten mindestens ein Polymer umfassen, das in mindestens einem Lösungsmittel gelöst ist, und wobei die Lösung eine im Wesentlichen homogene Lösung ist, wobei mindestens eine der Phasen, die auf der Innenfläche abgesetzt werden, mindestens das Polymer umfassen und wobei der Schritt des Stabilisierens der abgesetzten Phase die Gelbildung derselben umfasst.

7. Verfahren nach Anspruch 6, wobei das Phasentrennungsmittel aus der Gruppe ausgewählt ist bestehend aus Licht, pH-Wert, Initiatoren, Änderung der Temperatur, Bildung eines chemischen Produkts innerhalb der Form, Änderungen der kationischen und/oder anionischen Konzentrationen, elektrischen und magnetischen Feldern.

8. Verfahren nach Anspruch 6, wobei die Gelbildung durch Aussetzen einem Mittel gegenüber erreicht wird, das aus der Gruppe ausgewählt ist Licht, pH-Wert, Initiatoren, Änderung der Temperatur, Bildung eines chemischen Produkts innerhalb der Form, Änderungen der kationischen und/oder anionischen Konzentrationen, elektrischen und magnetischen Feldern.

9. Verfahren nach den Ansprüchen 3 oder 6, wobei die hohle Form eine zylindrische Röhre ist, derart, dass das Produkt eine polymere Röhre ist.

10. Verfahren nach Anspruch 9, wobei die zylindrische Röhre vorgewählte Oberflächenmerkmale auf der Innenfläche der zylindrischen Röhre umfasst.

11. Verfahren nach den Ansprüchen 1 oder 2 umfassend das Einsetzen einer porösen Struktur in die Form vor dem Füllen der Form mit der Lösung und wobei das Produkt schichtförmig auf eine Außenfläche der porösen Struktur aufgebracht wird.

12. Verfahren nach den Ansprüchen 3 oder 6, wobei die Lösung ein Vernetzungsmittel umfasst.

13. Verfahren nach Anspruch 12, wobei das Vernetzungsmittel aus der Gruppe ausgewählt ist bestehend aus einem multifunktionellen Methacrylat, Acrylat, Acrylamid, Methacrylamid, 1,5-Hexadien-3,4-diol, multifunktionellen 1,5-Hexadien-(HD-)Sternpolymeren von Poly(ethylenoxid).

14. Verfahren nach Anspruch 3, wobei das Monomer aus der Gruppe ausgewählt ist bestehend aus Acrylaten, Methacrylaten, Acrylsäure, Methacrylsäure, Acrylamid, Methacrylamid und Derivaten derselben; N-Vinylpyrrolidon, Acenaphthalin, N-Vinylacetamid, Phenylacetylen, Acrolein, Methylacrolein, N-Vinylpyridin, Vinylacetat, Vinylchlorid, Vinylfluorid, Vinylmethylketon, Vinylidenchlorid, Styrol und Derivaten desselben, Propen, Acrylnitril, Methacrylnitril, Acryloylchlorid, Allylacetat, Allylchlorid, Allylbenzol, Butadien und Derivaten derselben, N-Vinylcaprolactam, N-Vinylcarbazol, Cinnamaten und Derivaten derselben, Citraconimid und Derivaten desselben, Crotonsäure, Diallylphthalat, Ethylen und Derivaten desselben; Fumaraten und Derivaten derselben, Hexen und Derivaten desselben, Isopren und Derivaten desselben; Itaconat und Derivaten desselben; Itaconamid und Derivaten desselben; Diethylmaleat, 2-(Acryloyloxy)ethyldiethylphosphat, Vinylphosphonaten und Derivaten derselben; Maleinsäureanhydrid, Maleimid, Siliconmonomeren und Derivaten derselben und irgendeiner Kombination derselben.

15. Verfahren nach Anspruch 3 oder 6, wobei das Lösungsmittel aus der Gruppe ausgewählt ist bestehend aus nucleophilen oder elektrophilen Molekülen ausgewählt aus der Gruppe bestehend aus Wasser, Alkoholen, Ethylenglykol, Ethanol, Aceton, Poly(ethylenglykol), Dimethylsulfoxid, Dimethylformamid, Alkanen und Derivaten derselben, Acetonitril, Essigsäure, Benzol, Essigsäureanhydrid, Benzylacetat, Tetrachlorkohlenstoff, Chlorbenzol, n-Butanol, 2-Chlorethanol, Chloroform, Cyclohexan, Cyclohexanol, Dichlormethan, Diethylether, Di(ethylenglykol), Di(ethylenglykol)monomethylether, 1,4-Dioxan, N,N'-Dimethylacetamid, N,N'-Dimethylformamid, Ethylacetat, Formaldehyd, n-Heptan, Hexachlorethan, Hexan, Isobutanol, Isopropanol, Methanol, Methylethylketon, Nitrobenzol, n-Octan, n-Pentanol, Propylacetat, Propylenglykol, Pyridin, Tetrahydrofuran, Toluol, Trichlorethylen, o-Xylol und p-Xylol, einem Monomer, einem flüssigen Vernetzungsmittel oder Mischungen derselben.

16. Verfahren nach Anspruch 3, wobei das Lösungsmittel das Monomer, jedoch kein Polymer oder aus dem Monomer gebildetes vernetztes Polymer löslich macht.

17. Verfahren nach Anspruch 3, wobei mindestens ein Monomer im Bereich von circa 0,001 Gew.-% bis circa 60 Gew.-% vorliegt.

18. Verfahren nach Anspruch 6, wobei das Polymer aus der Gruppe ausgewählt ist bestehend aus Polyacrylaten, Polysulfonen, Peptidsequenzen, Proteinen, Oligopeptiden, Collagen, Fibronectin, Laminin, Polymethacrylaten, Polyacetaten, Polyestern, Polyamiden, Polycarbonaten, Polyanhydriden, Polyaminosäuren, Cellulose, Hyaluronsäure, Natriumhyaluronat, Alginat, Agarose, Chitosan, Chitin und Mischungen derselben.

19. Verfahren nach Anspruch 1 umfassend das physikalische oder chemische Modifizieren der Innenfläche der Form auf der durch Induzieren der Perlbildung oder des Ausbreitens der abgetrennten flüssigen Phase vorgewählte Morphologien in die Wand des Produkts induziert werden.

20. Verfahren nach Anspruch 19 mit Molekülen, die Silaniermittel umfassen.

21. Verfahren nach den Ansprüchen 3 oder 6, einschließlich des Schritts des Entfernens des Lösungsmittels und einschließlich des Wiederholens der Schritte a), b) und c) mindestens einmal zur Bildung eines mehrschichtigen Produkts.

22. Verfahren nach Anspruch 19, wobei die vorgewählten Wandmorphologien aus einer Gruppe ausgewählt sind bestehend aus einer porösen Struktur, einer Gelstruktur und überlappenden Bereichen einer porösen/Gelstruktur.

23. Verfahren nach Anspruch 19, wobei die vorgewählten Wandmorphologien eine überwiegende Gelmorphologie mit porösen Kanälen umfassen, die von einer Peripherie zu einer Lumenseite führen, was zur Fleckenbildung auf einer äußeren Wandfläche führt.

24. Verfahren nach Anspruch 19, wobei die Wandstruktur als Reservoir für die Abgabe von Arzneimitteln, Therapeutika, Zellen, Zellprodukten, Genen, Virenvektoren, Proteinen, Peptiden, Hormonen, Kohlehydraten, Wachstumsfaktoren verwendet werden.

25. Verfahren nach Anspruch 1, wobei die Lösung Mikrosphären enthält, die vorgewählte Bestandteile enthalten, und wobei das Produkt die Mikrosphären entweder gleichförmig verteilt oder in einem Gradienten innerhalb der Wandstruktur des Produkts enthält.

26. Verfahren nach Anspruch 12, wobei das Vernetzungsmittel aus der Gruppe ausgewählt ist bestehend aus Ethylenglykoldimethacrylat (EDMA), Hexamethylendimethacrylat (HDMA), Poly(ethylenglykol)dimethacrylat, 2,3-Dihydroxybutandiol-1,4-dimethacrylat (BHDMA) und 1,4-Butandioldimethacrylat (BDMA).

27. Verfahren nach Anspruch 3, wobei das Monomer aus der Gruppe ausgewählt ist bestehend aus 2-Hydroxyethylmethacrylat, Methylmethacrylat, 2-Polyethylenglykolethylmethacrylat, Ethylacrylat, 2-Hydroxyethylacrylat, 2-Chlorethylmethacrylat, Butylmethacrylat, Glycidylmethacrylat, Hydroxypropylmethacrylat; Hydroxypropylmethacrylamid, N,N-Diethylacrylamid, N,N-Dimethylacrylamid, 2-Chlorethylacrylamid, 2-Nitrobutylacrylamid; 1,1-Diphenylethylen, Chlortrifluorethylen, Dichlorethylen, Tetrachlorethylen; Isopropenylacetat, Isopropenylmethylketon, Isopropenylisocyanat; und Kombinationen derselben.

28. Verfahren nach Anspruch 6, wobei das Polymer aus der Gruppe ausgewählt ist bestehend aus Poly(methylmethacrylat), Poly(ethoxyethylmethacrylat), Poly(hydroxyethylmethacrylat); Poly(N-vinylpyrrolidon), Polyvinylacetat, Polyvinylalkohol, Poly(hydroxypropylmethacrylamid), Poly(caprolacton), Poly(dioxanon)polyglykolsäure, Polymilchsäure, Copolymeren von Milch- und Glykolsäuren und Polytrimethylencarbonaten, Poly(butadien), Polystyrol, Polyacrylnitril, Poly(chloropren), Neopren, Poly(isobuten), Poly(isopren), Polypropylen, Polytetrafluorethylen, Poly (vinylidenfluorid), Poly(chlortrifluorethylen), Poly(vinylchlorid), Poly(oxymethylen), Poly(ethylenterephthalat), Poly (oxyethylen)poly(oxyterephthaloyl); Poly[imino(1-oxohexamethylen)], Poly(iminoadipoyliminohexamethylen), Poly (iminohexamethyleniminosebacoyl), Poly[imino(1-oxodeodcamethylen)] und Mischungen derselben.

Revendications

1. Procédé de production d'un produit, comprenant les étapes consistant à :

   a) remplir un intérieur d'un moule (A) avec une solution (E) de façon à ce que sensiblement tout l'air soit déplacé de celui-ci, la solution (E) comprenant au moins deux composants dont les phases peuvent être séparées au moyen d'un agent de séparation des phases en au moins deux phases ;
   b) faire pivoter ledit moule (A) contenant ladite solution (E) à une vitesse de rotation efficace en présence dudit agent de séparation des phases de façon à induire une séparation des phases entre lesdits au moins deux composants en au moins deux phases de sorte que sous la rotation, au moins une des phases (J) se dépose sur une surface interne (K) du moule (A) ; et
   c) former ledit produit en stabilisant ladite au moins une des phases (J) déposée sur la surface interne (K) du moule (A).

2. Procédé selon la revendication 1, comprenant l'étape consistant à extraire ledit produit dudit moule.

3. Procédé selon les revendications 1 ou 2, dans lequel lesdits au moins deux composants comprennent au moins un monomère et au moins un solvant, et dans lequel ladite solution est une solution sensiblement homogène, dans lequel ladite au moins une des phases qui se dépose sur la surface interne comprend au moins le monomère, et dans lequel l'étape consistant à stabiliser ladite phase déposée comprend la gélification du monomère par polymérisation de celui-ci.

4. Procédé selon la revendication 3, dans lequel ledit agent de séparation des phases est choisi dans le groupe constitué par la lumière, le pH, les agents d'initiation, le changement de température, la création d'un produit chimique dans le moule, les changements de concentrations cationiques et/ou anioniques, les champs électriques et magnétiques.

5. Procédé selon la revendication 4, dans lequel ledit agent d'initiation est choisi dans le groupe constitué par les initiateurs de radicaux libres les initiateurs thermiques et les photo-initiateurs ainsi que les initiateurs redox.

6. Procédé selon les revendications 1 ou 2, dans lequel lesdits au moins deux composants comprennent au moins un polymère dissous dans au moins un solvant et dans lequel ladite solution est une solution sensiblement homogène, dans lequel ladite au moins une des phases qui se dépose sur la surface interne comprend au moins le polymère, et dans lequel l'étape consistant à stabiliser ladite phase déposée comprend la gélification de celle-ci.

7. Procédé selon la revendication 6, dans lequel ledit agent de séparation des phases est choisi dans le groupe constitué par la lumière, le changement de pH, le changement de température, la création d'un produit chimique dans le moule, les changements de concentrations cationiques et/ou anioniques, les champs électriques et magnétiques.

8. Procédé selon la revendication 6, dans lequel la gélification est obtenue par exposition à un agent choisi dans le groupe constitué par la lumière, le changement de pH, le changement de température, la création d'un produit chimique dans le moule, les changements de concentrations cationiques et/ou anioniques, les champs électriques et magnétiques.

9. Procédé selon les revendications 3 ou 6, dans lequel ledit moule creux est un tube cylindrique de sorte que ledit produit est un tube polymère.

10. Procédé selon la revendication 9, dans lequel ledit tube cylindrique comprend des attributs de surface présélectionnés sur ladite surface interne du tube cylindrique.

11. Procédé selon les revendications 1 ou 2, comprenant l'étape consistant à insérer une structure poreuse dans ledit moule avant de remplir ledit moule avec ladite solution, et dans lequel ledit produit est enduit sur une surface externe de ladite structure poreuse.

12. Procédé selon les revendications 3 ou 6, dans lequel ladite solution comprend un agent de réticulation.

13. Procédé selon la revendication 12, dans lequel l'agent de réticulation est choisi dans le groupe constitué par le méthacrylate multifonctionnel, l'acrylate, l'acrylamide, le méthacrylamide, le 1,5-hexadiène-3,4-diol, le 1,5-hexadiène (HD), les polymères en étoile multifonctionnels du poly(oxyde d'éthylène).

14. Procédé selon la revendication 3, dans lequel ledit monomère est choisi dans le groupe constitué par les acrylates, les méthacrylates, l'acide acrylique, l'acide méthacrylique, l'acrylamide, le méthacrylamide et leurs dérivés ; la N-vinylpyrrolidone, l'acénaphtalène, le N-vinylacétamide, le phénylacétylène, l'acroléine, la méthylacroléine, la N-vinylpyridine, l'acétate de vinyle, le chlorure de vinyle, le fluorure de vinyle, la vinylméthylcétone, le chlorure de vinylidène, le styrène et leurs dérivés, le propène, l'acrylonitrile, le méthacrylonitrile, le chlorure d'acryloyle, l'acétate d'allyle, le chlorure d'allyle, l'alkylbenzène, le butadiène et leurs dérivés, le N-vinylcaprolactame, le N-vinylcarbazole, les cinnamates et leurs dérivés, le citraconimide et leurs dérivés, l'acide crotonique, le phtalate de diallyle, l'éthylène et leurs dérivés ; les fumarates et leurs dérivés, l'hexène et ses dérivés, l'isoprène et ses dérivés ; l'itaconate et ses dérivés ; l'itaconamide et ses dérivés ; le diéthylmaléate, le diéthylphosphate de 2-(acryloyloxy)éthyle, les vinylphosphonates et leurs dérivés, l'anhydride maléique, le maléimide, les monomères de silicone et leurs dérivés ; et une quelconque combinaison de ceux-ci.

15. Procédé selon la revendication 3 ou 6, dans lequel ledit solvant est choisi dans le groupe constitué par les molécules nucléophiles ou électrophiles choisies dans le groupe constitué par l'eau, les alcools, l'éthylène glycol, l'éthanol, l'acétone, le poly(éthylène glycol), le diméthylsulfoxyde, le diméthylformamide, les alcanes et leurs dérivés, l'acétonitrile, l'acide acétique, le benzène, l'anhydride acétique, l'acétate de benzyle, le tétrachlorure de carbone, le chlorobenzène, le n-butanol, le 2-chloroéthanol, le chloroforme, le cyclohexane, le cyclohexanol, le dichlorométhane, l'éther diéthylique, le di(éthylène glycol), l'éther monométhylique de di(éthylène glycol), le 1,4-dioxane, le N,N-diméthylacétamide, le N,N-diméthylformamide, l'acétate d'éthyle, le formaldéhyde, le n-heptane, l'hexachloroétha-

ne, l'hexane, l'isobutanol, l'isopropanol, le méthanol, la méthyléthylcétone, le nitrobenzène, le n-octane, le n-pentanol, l'acétate de propyle, le propylène glycol, la pyridine, le tétrahydrofuranne, le toluène, le trichloroéthylène, l'o-xylène et le p-xylène, un monomère, un agent de réticulation liquide ou leurs mélanges.

16. Procédé selon la revendication 3, dans lequel ledit solvant solubilise ledit monomère mais pas un polymère ou un polymère réticulé formé à partir dudit monomère.

17. Procédé selon la revendication 3, dans lequel ledit au moins un monomère est présent dans une gamme allant d'environ 0,001 % en poids à environ 60 % en poids.

18. Procédé selon la revendication 6, dans lequel ledit polymère est choisi dans le groupe constitué par les polyacrylates, les polysulfones, les séquences peptidiques, les protéines, les oligopeptides, le collagène, la fibronectine, la laminine, les polyméthacrylates, les polyacétates, les polyesters, les polyamides, les polycarbonates, les polyanhydrides, les acides polyamino, la cellulose, l'acide hyaluronique, le hyaluronate de sodium, l'alginate, l'agarose, le chitosane, la chitine et leurs mélanges.

19. Procédé selon la revendication 1, comprenant l'étape consistant à modifier physiquement ou chimiquement la surface interne du moule sur lequel des morphologies présélectionnées sont induites dans la paroi dudit produit en induisant un sertissage et une enduction de la phase liquide séparée.

20. Procédé selon la revendication 19, les molécules comprenant des agents réactifs au silane.

21. Procédé selon les revendications 3 ou 6, comprenant l'étape consistant à extraire le solvant et à inclure les étapes répétitives a), b) et c), au moins une fois pour produire un produit multicouche.

22. Procédé selon la revendication 19, dans lequel les morphologies de paroi présélectionnées sont choisies dans un groupe constitué par une structure poreuse, une structure gélifiée et des régions chevauchantes de structure poreuse/gélifiée.

23. Procédé selon la revendication 19, dans lequel les morphologies de paroi présélectionnées comprennent une morphologie essentiellement gélifiée avec des canaux poreux s'étendant depuis une périphérie jusqu'à un côté luminal, entraînant la formation de taches sur une surface latérale externe.

24. Procédé selon la revendication 19, dans lequel la structure latérale est utilisée comme réservoir pour l'administration de médicaments, produits thérapeutiques, cellules, produits cellulaires, gènes, vecteurs viraux, protéines, peptides, hormones, glucides, facteurs de croissance.

25. Procédé selon la revendication 1, dans lequel la solution contient des microsphères contenant des constituants présélectionnés et dans lequel le produit comprend lesdites microsphères réparties soit uniformément soit dans un gradient dans la structure latérale du produit.

26. Procédé selon la revendication 12, dans lequel l'agent de réticulation est choisi dans le groupe constitué par le diméthacrylate d'éthylène glycol (EDMA), le diméthacrylate d'hexaméthylène (HDMA), le diméthacrylate de poly (éthylène glycol), le 1,4-diméthacrylate de 2,3-dihydroxybutanediol (BHDMA) et le diméthacrylate de 1,4-butanediol (BDMA).

27. Procédé selon la revendication 3, dans lequel ledit monomère est choisi dans le groupe constitué par le méthacrylate de 2-hydroxyéthyle, le méthacrylate de méthyle, le méthacrylate d'éthyle de 2-polyéthylène glycol, l'acrylate d'éthyle, l'acrylate de 2-hydroxyéthyle, le méthacrylate de 2-chrloréthyle, le méthacrylate de butyle, le méthacrylate de glycidyle, le méthacrylate d'hydroxypropyle ; le méthacrylamide d'hydroxypropyle, l'acrylamide de N,N-diéthyle, l'acrylamide de N,N-diméthyle, l'acrylamide de 2-chloroéthyle, l'acrylamide de 2-nitrobutyle ; le 1,1-diphényléthylène, le chlorotrifluoroéthylène, le dichloroéthylène, le tétrachloroéthylène ; l'acétate d'isopropényle, la méthylcétone d'isopropényle, l'isocyanate d'isopropényle ; et une quelconque combinaison de ceux-ci.

28. Procédé selon la revendication 6, dans lequel ledit polymère est choisi dans le groupe constitué par le poly(méthacrylate de méthyle), le poly(méthacrylate d'éthoxyéthyle), le poly(méthacrylate d'hydroxyéthyle) ; la poly(N-vinylpyrrolidone), l'acétate de polyvinyle, l'alcool polyvinylique, le poly(méthacrylamide d'hydroxypropyle), le poly(caprolactone), l'acide polyglycolique de poly(dioxanone), l'acide polylactique, les copolymères d'acides lactiques et gly-

coliques, et les carbonates de polytriméthylène, le poly(butadiène), le polystyrène, le polyacrylonitrile, le poly(chloroprène), le néoprène, le poly(isobutène), le poly(isoprène), le polypropylène, le polytétrafluoroéthylène, le poly (fluorure de vinylidène), le poly(chlorotrifluoroéthylène), le poly(chlorure de vinyle), le poly(oxyméthylène), le poly (éthylène téréphtalate), le poly(oxyéthylène), le poly(oxytéréphtaloyle) ; le poly[imino(1-oxohexaméthylène)], le poly (iminoadipoyliminohexaméthylène), le poly(iminohexaméthylène-iminosébacoyle), le poly[imino(1-oxododécaméthylène)], et leurs mélanges.

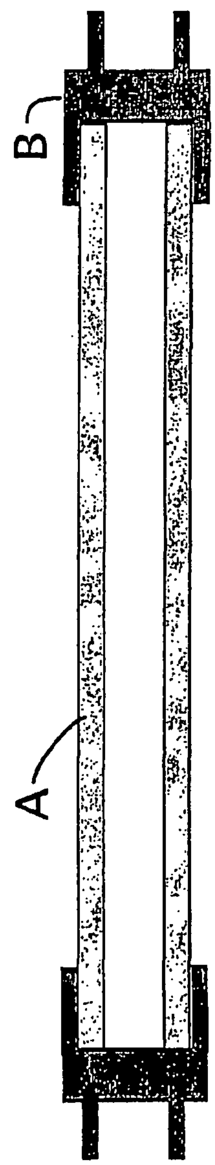


Fig.1a

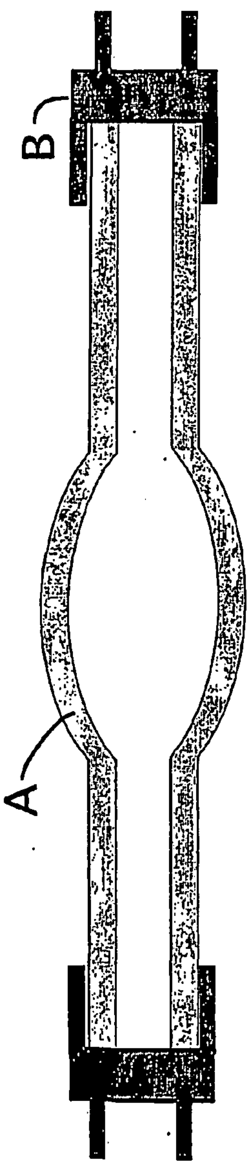


Fig.1b

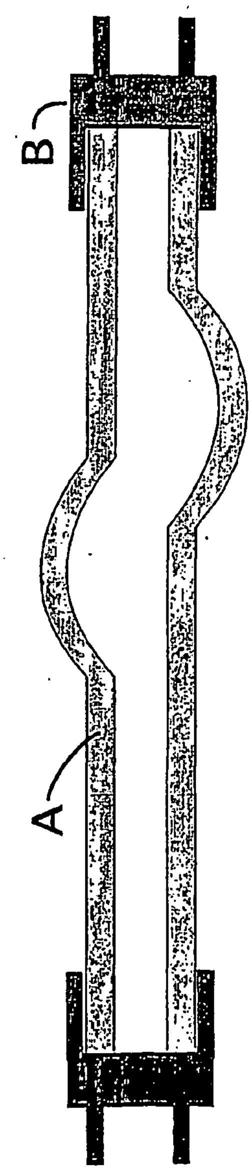


Fig.1c

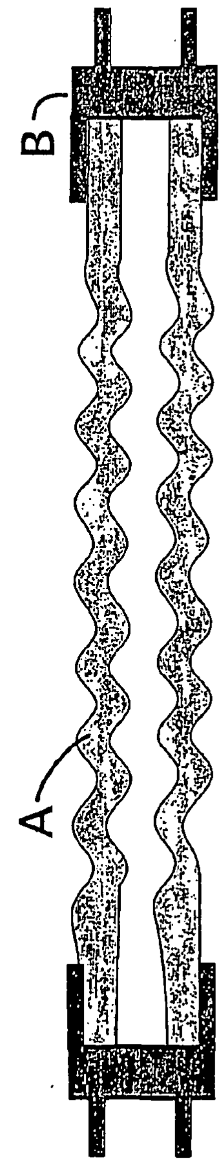


Fig.1d

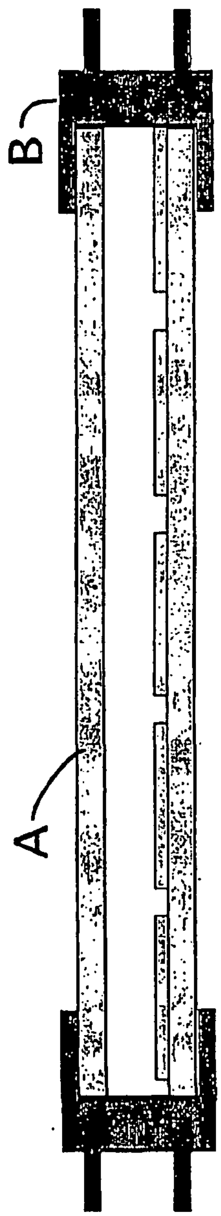


Fig.2a

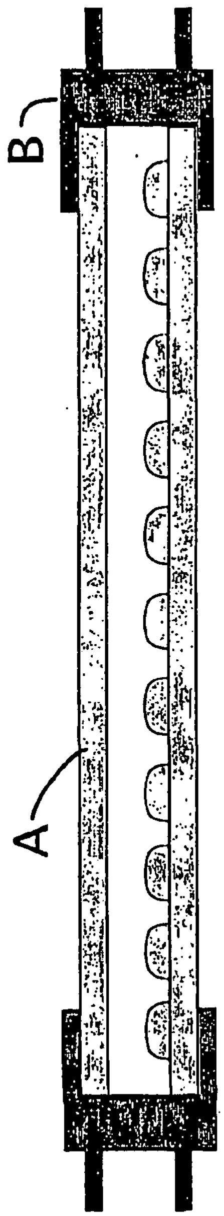


Fig.2b

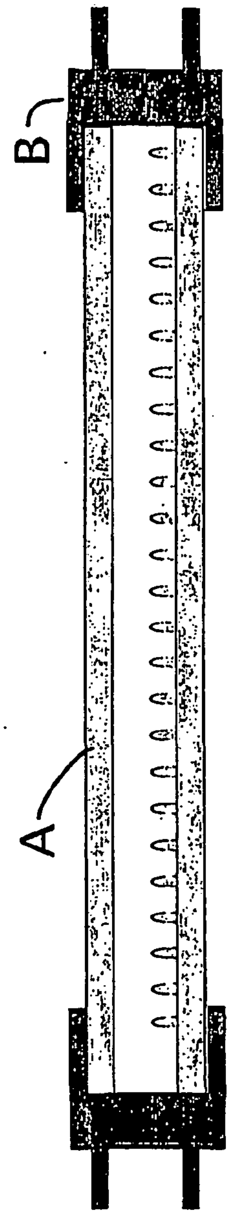


Fig.2c

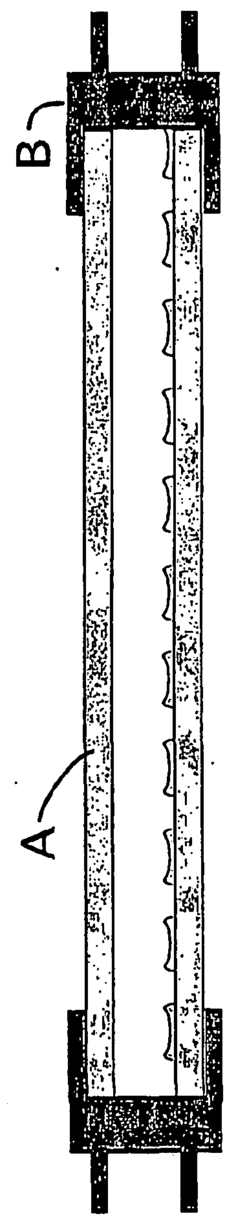


Fig.2d

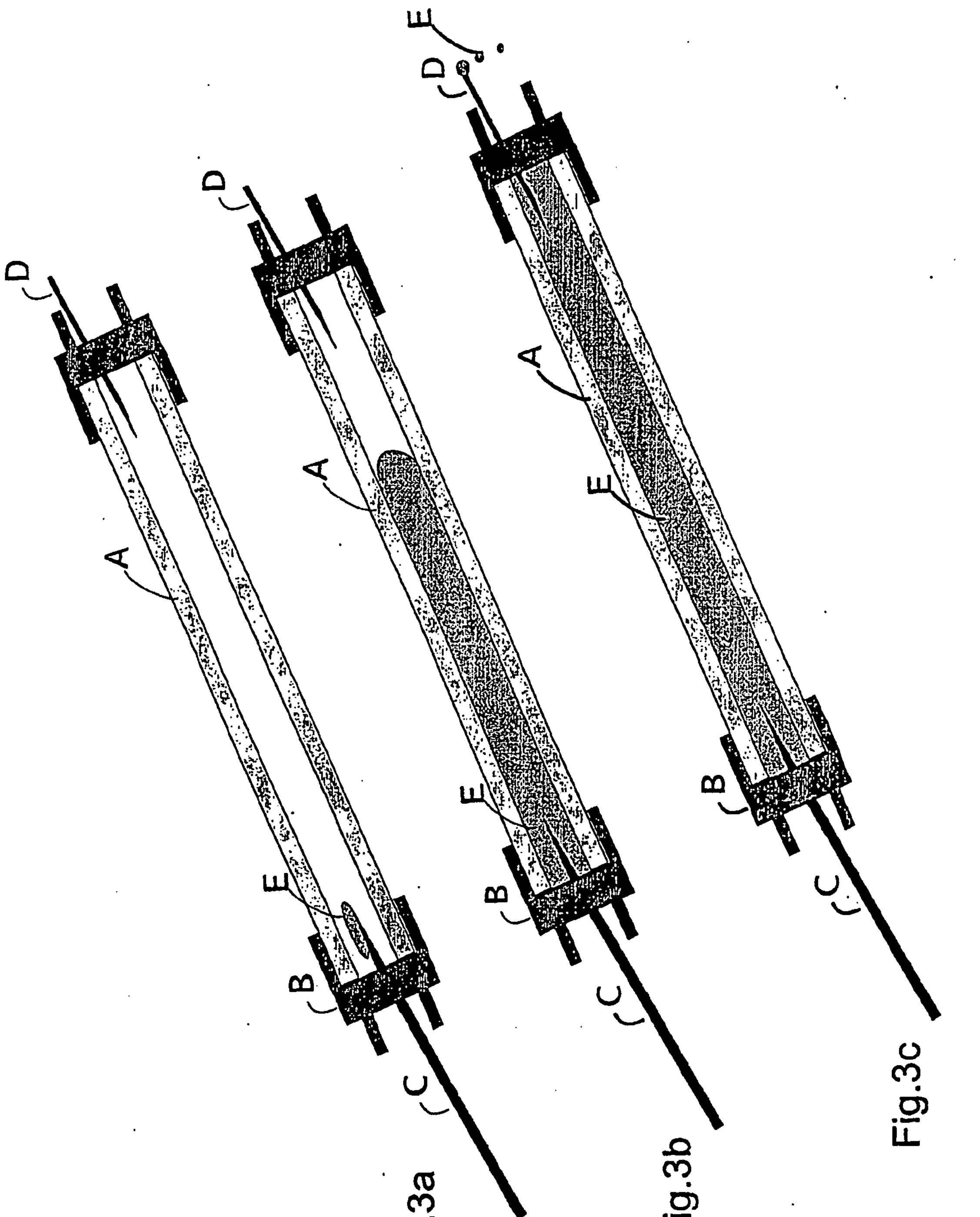


Fig.3a

Fig.3b

Fig.3c

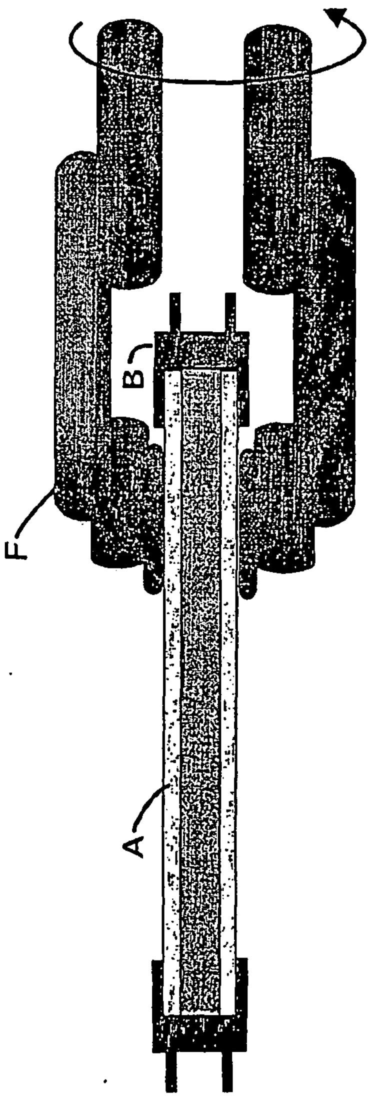


Fig.4a

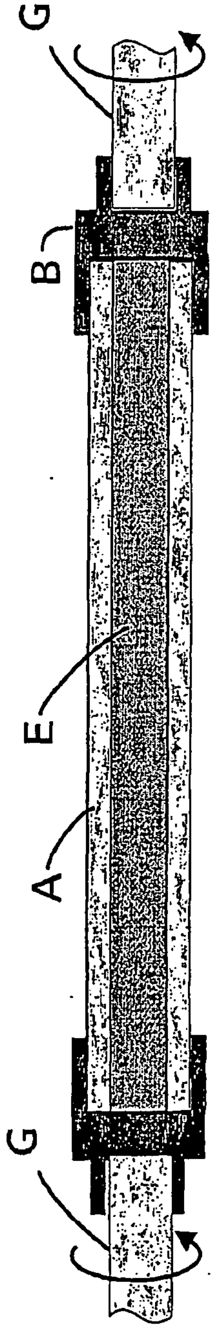


Fig.4b

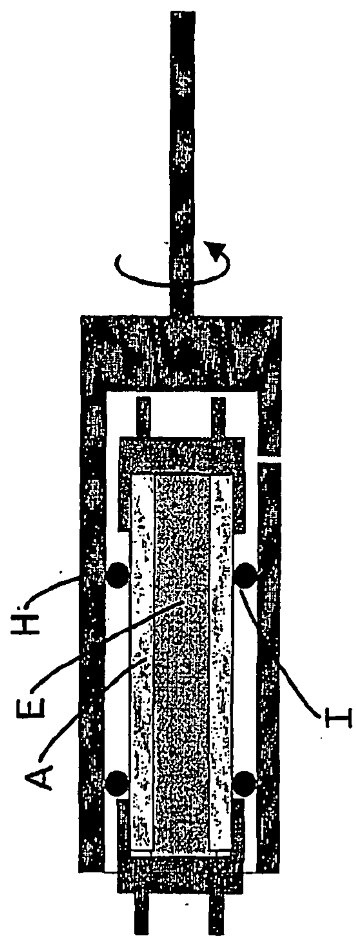


Fig.4c

Fig.5a

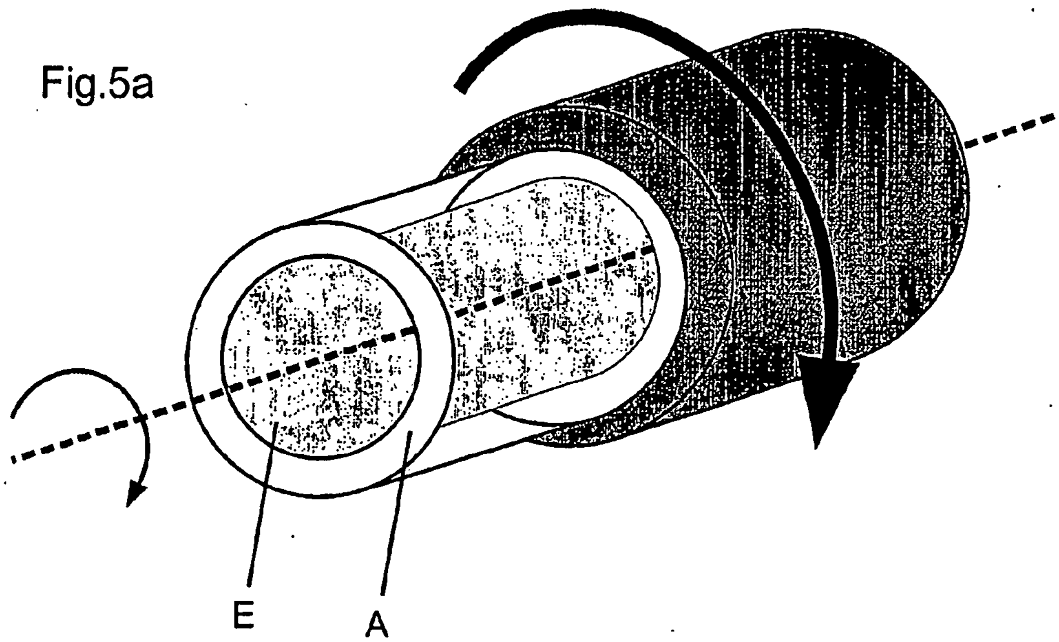
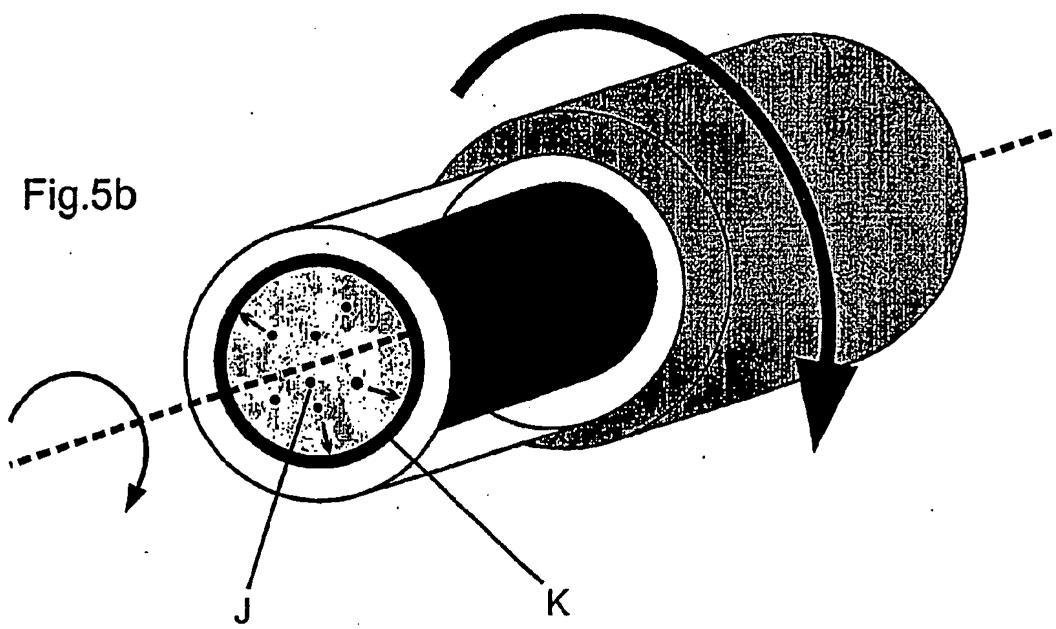


Fig.5b



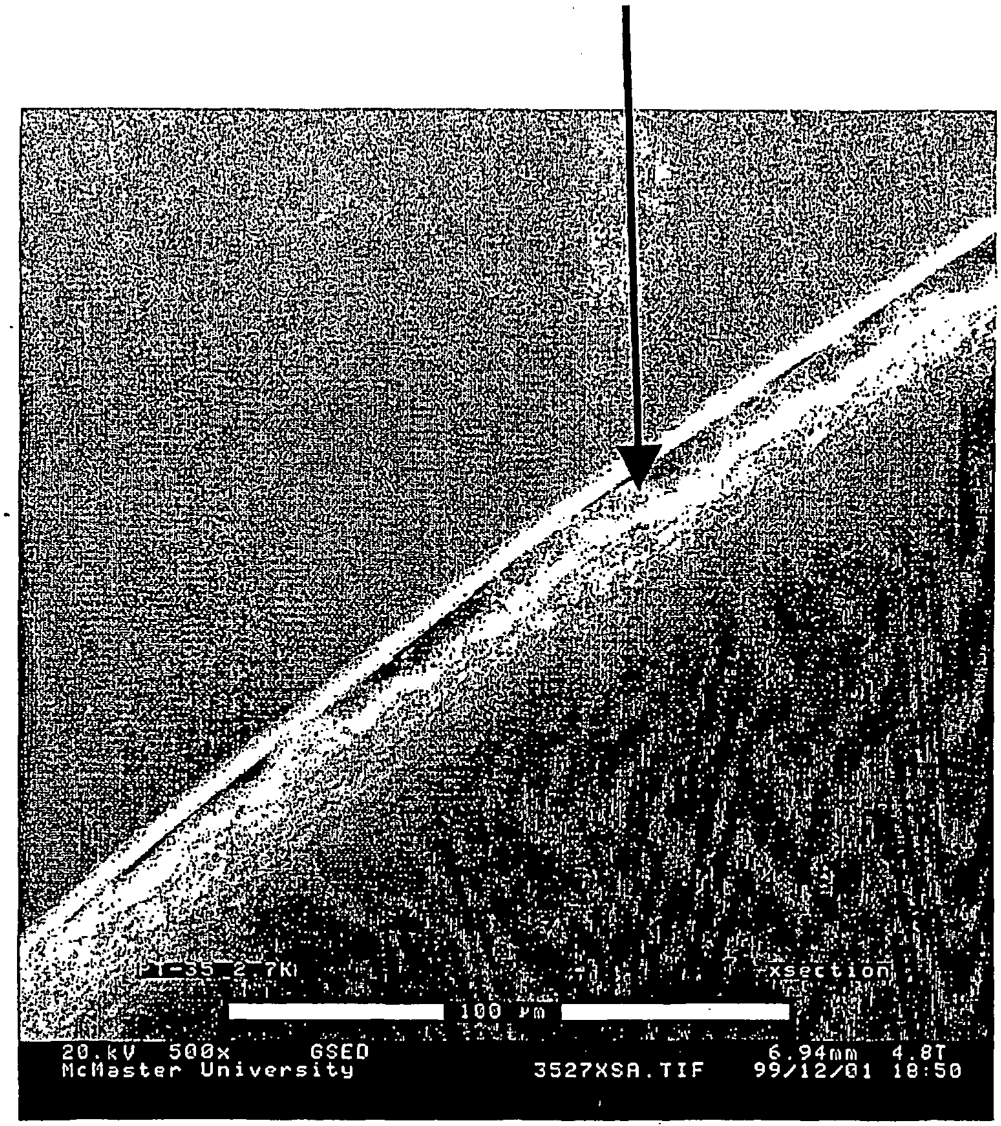

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Fig.6

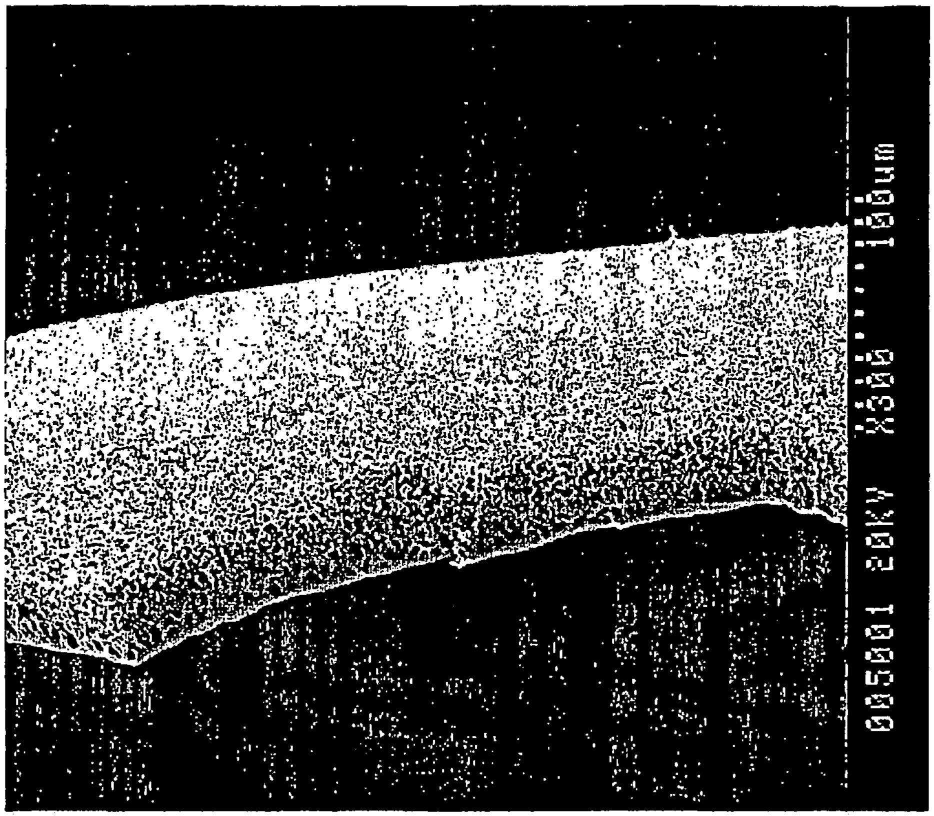


Fig.7b

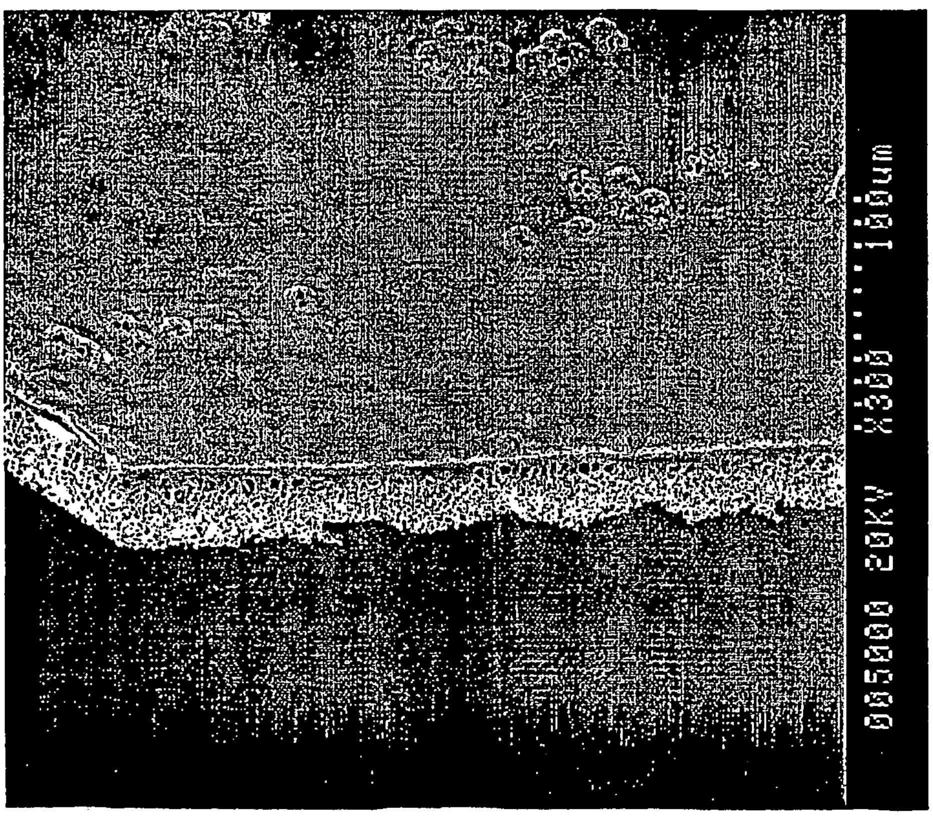
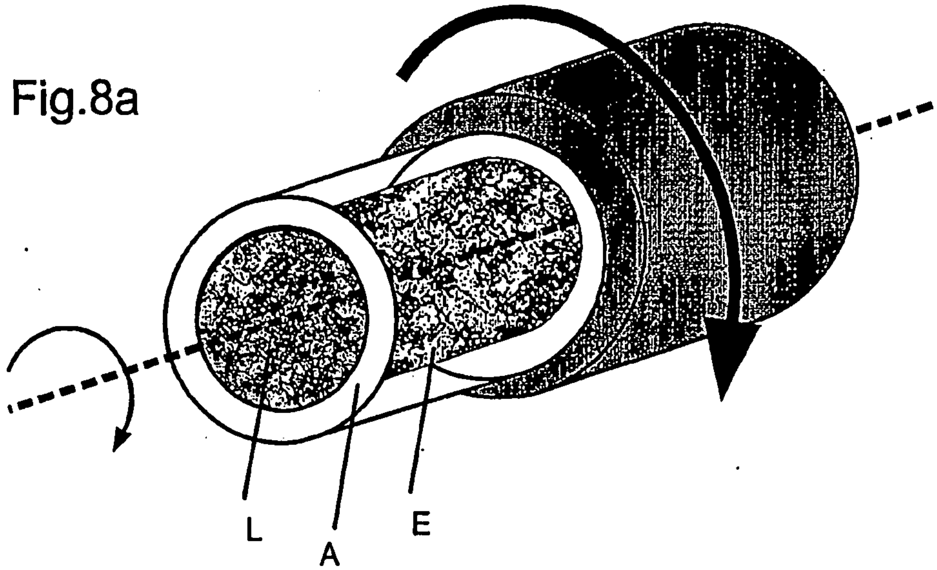


Fig.7a

Fig.8a



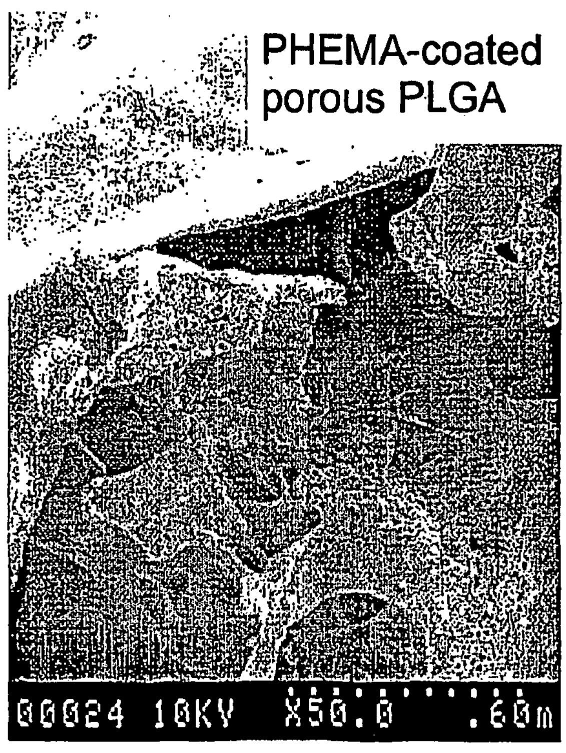


Fig.8b

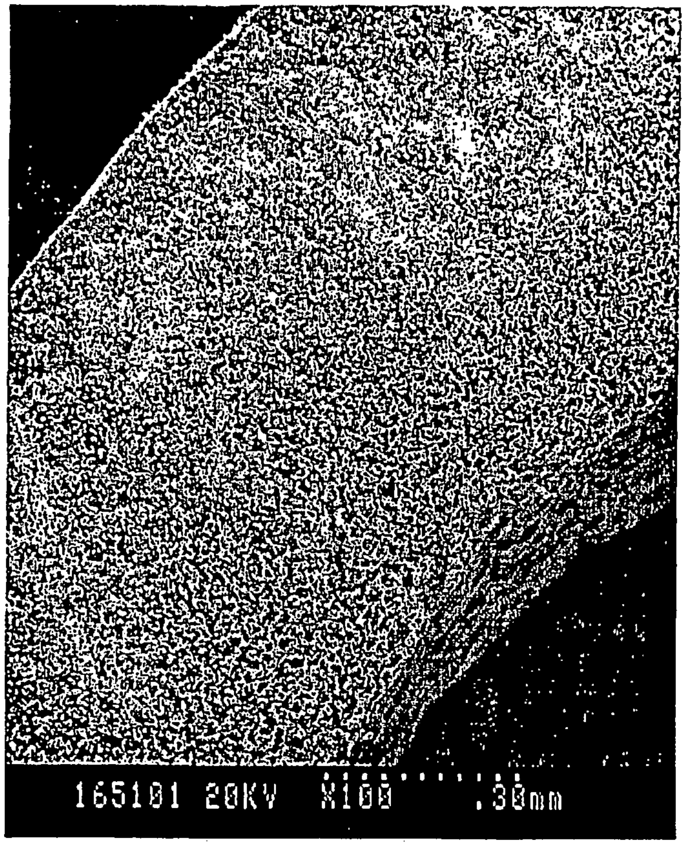


Fig.9a

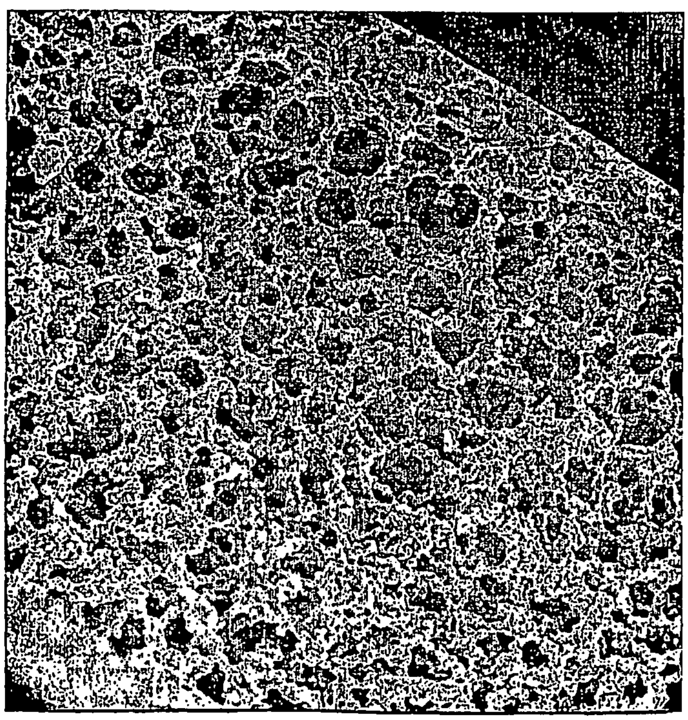


Fig.9b

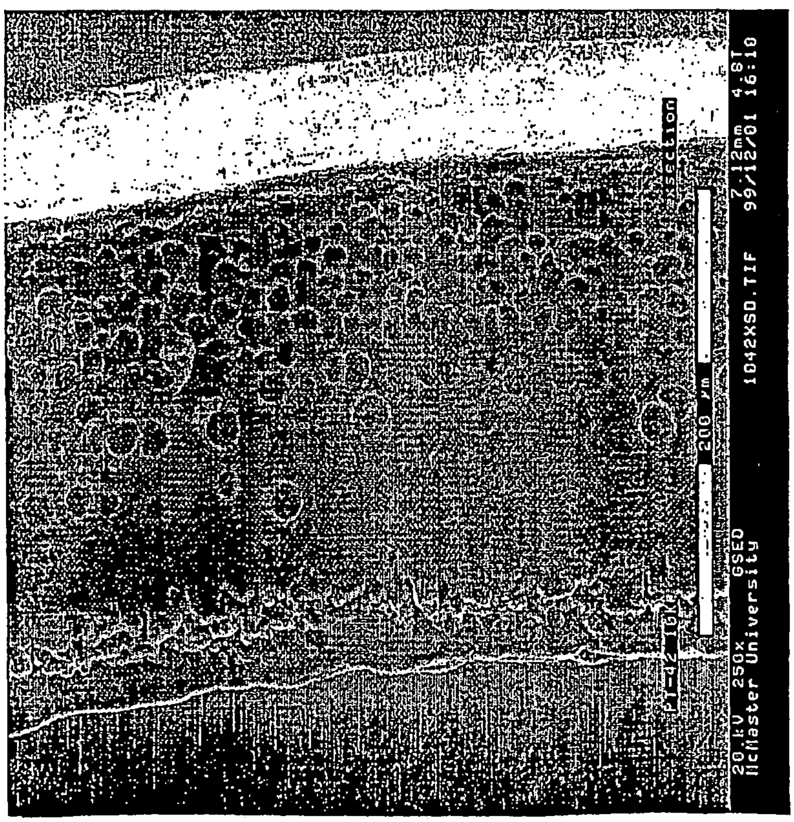


Fig.10a

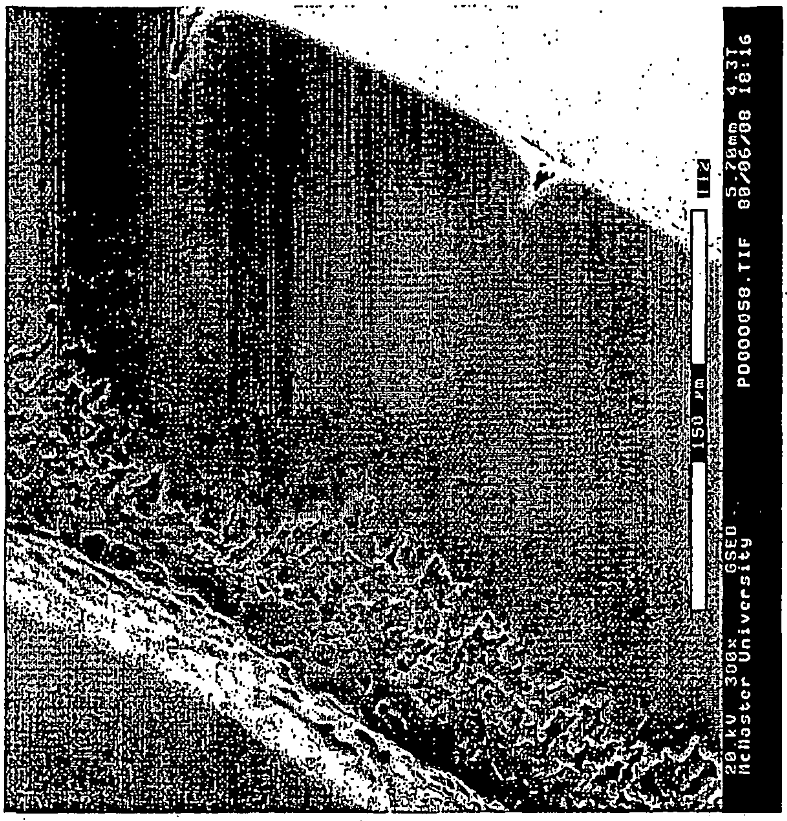


Fig.10b

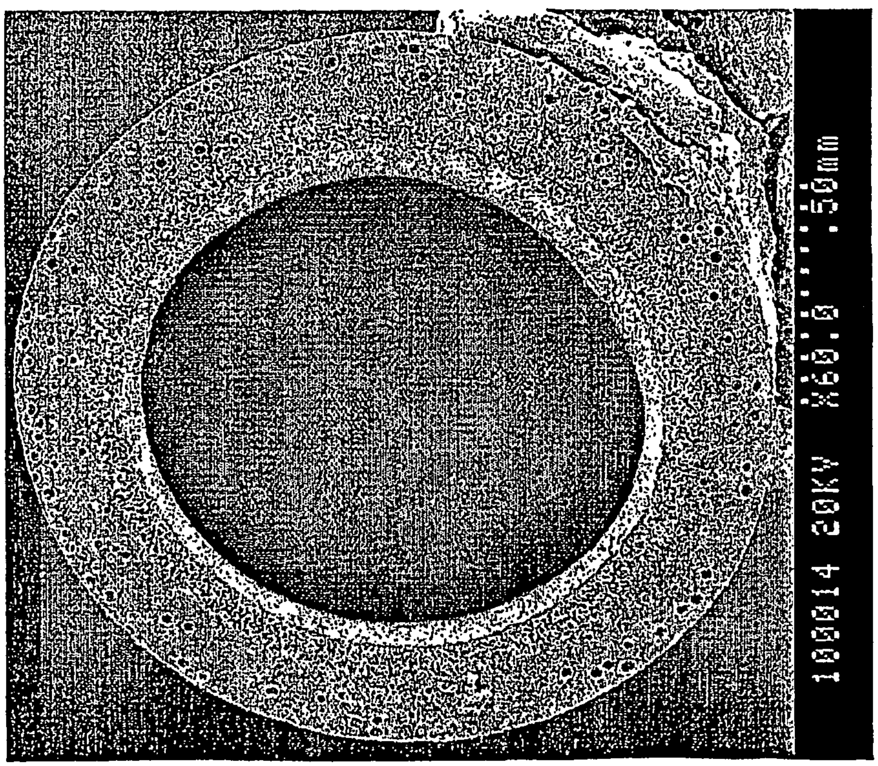


Fig.11a

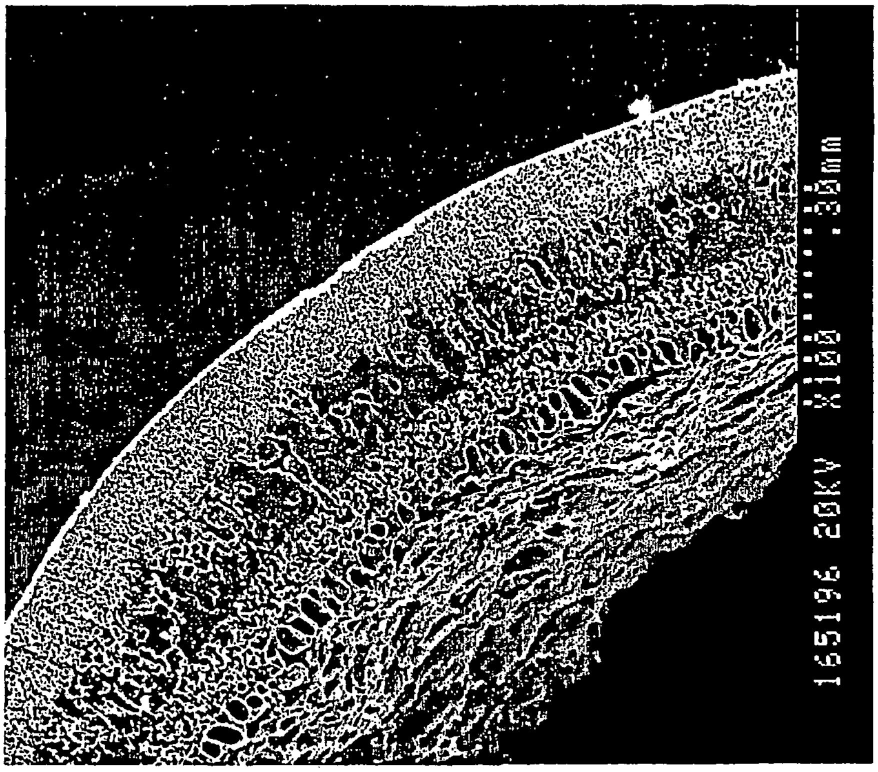


Fig.11b

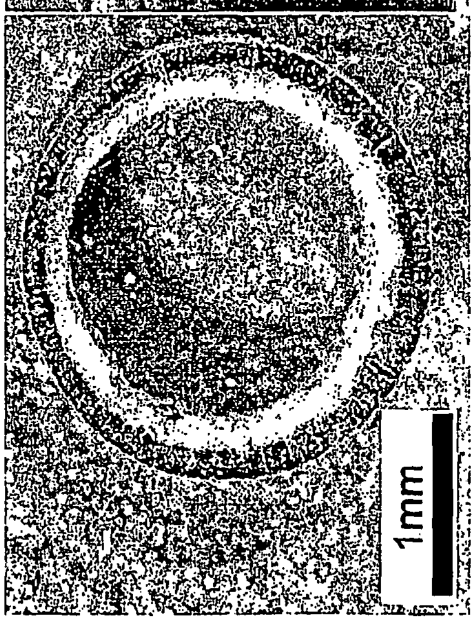


Fig.12a

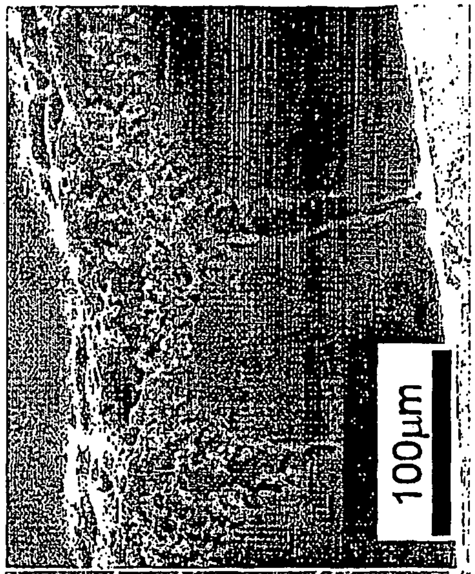


Fig.12b

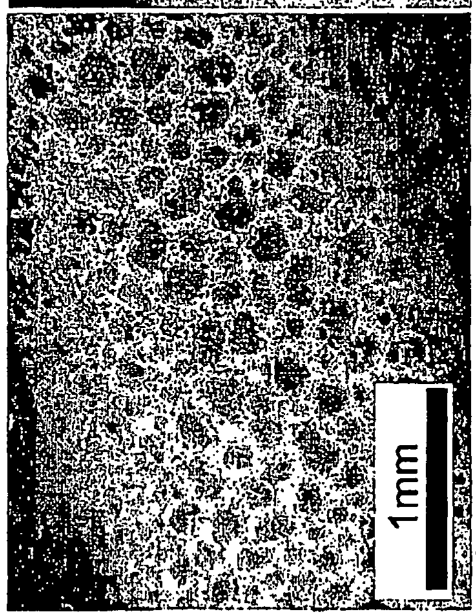


Fig.12c

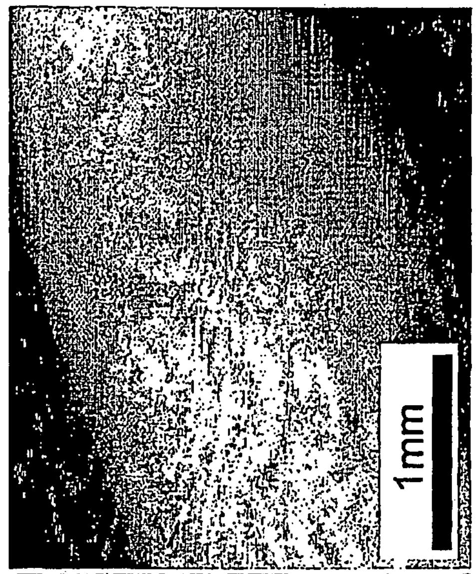


Fig.12d

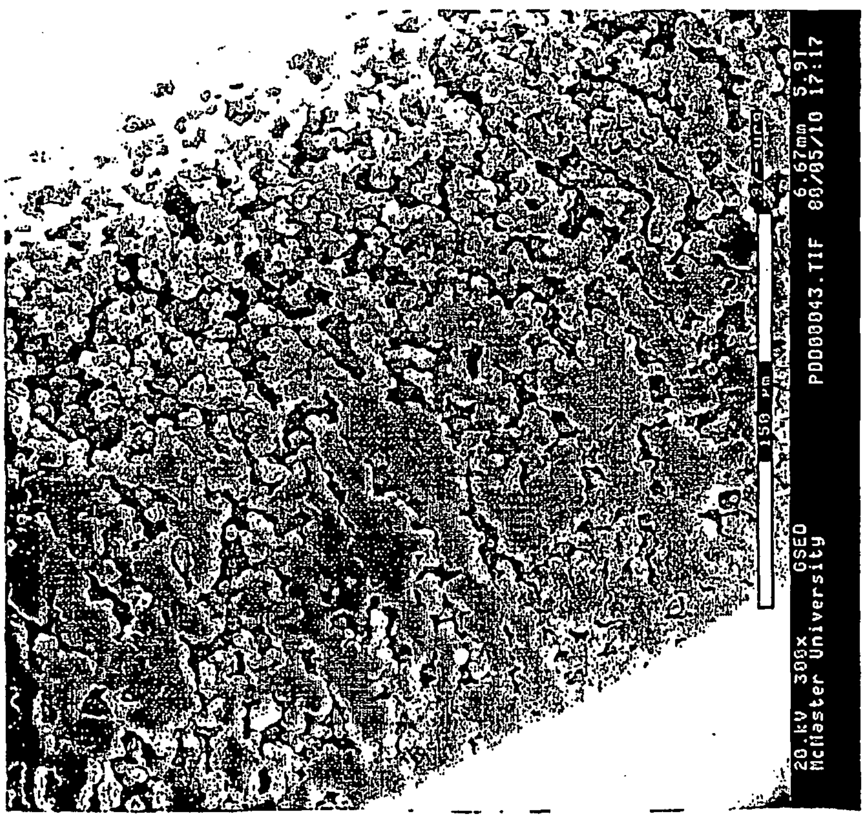


Fig13a

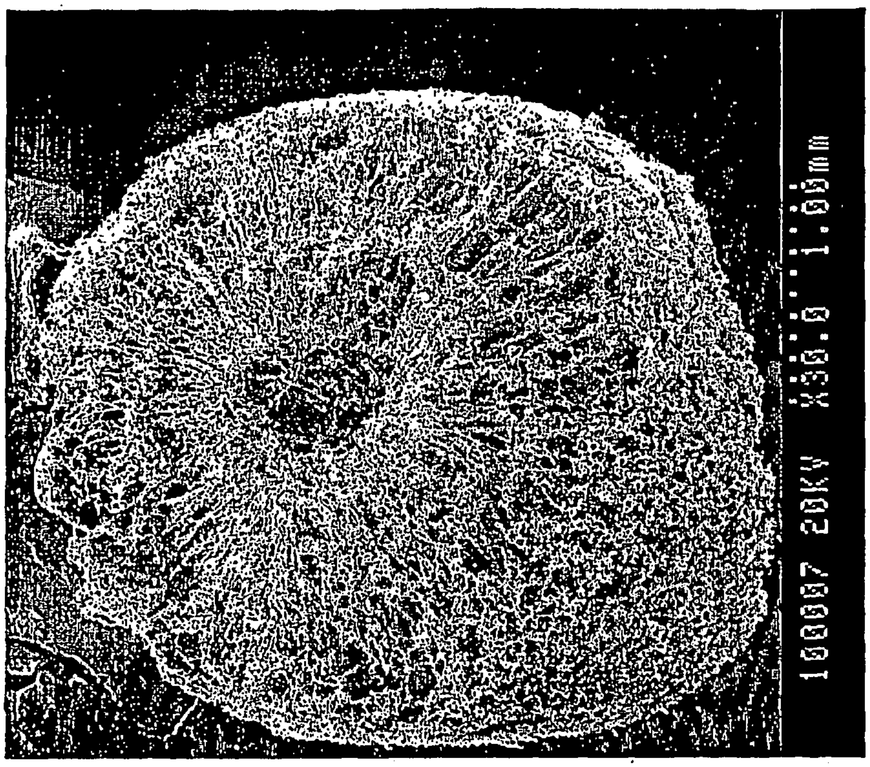


Fig13b

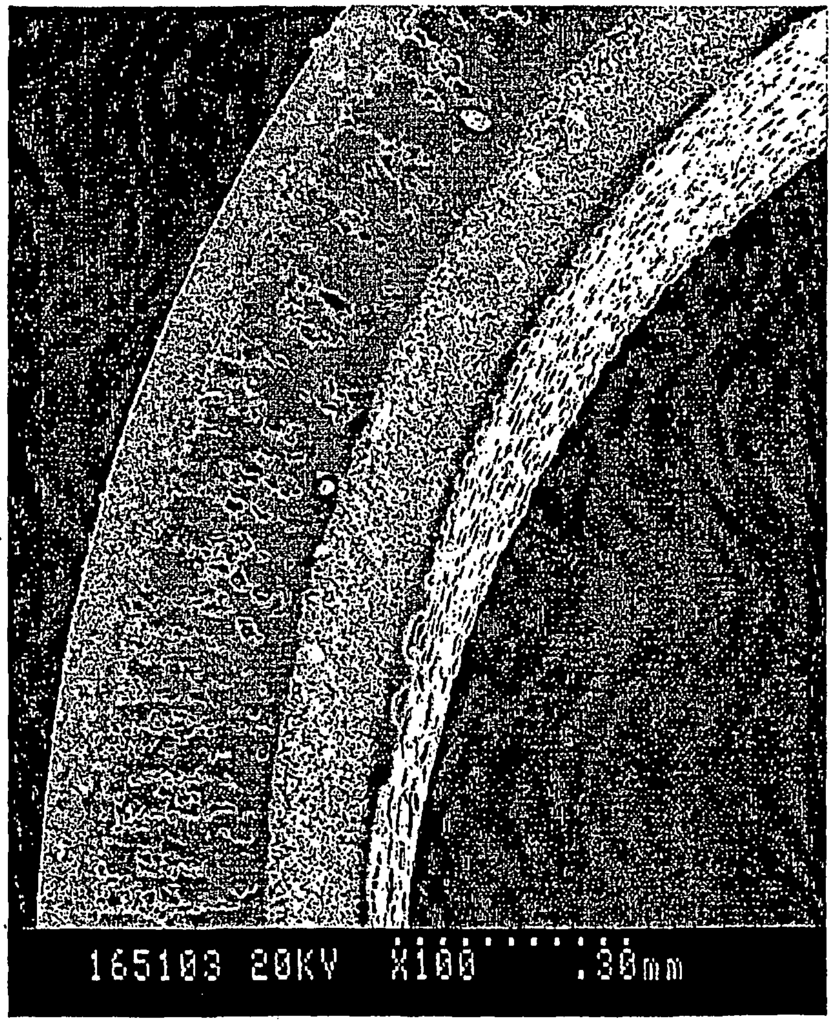


Fig.14

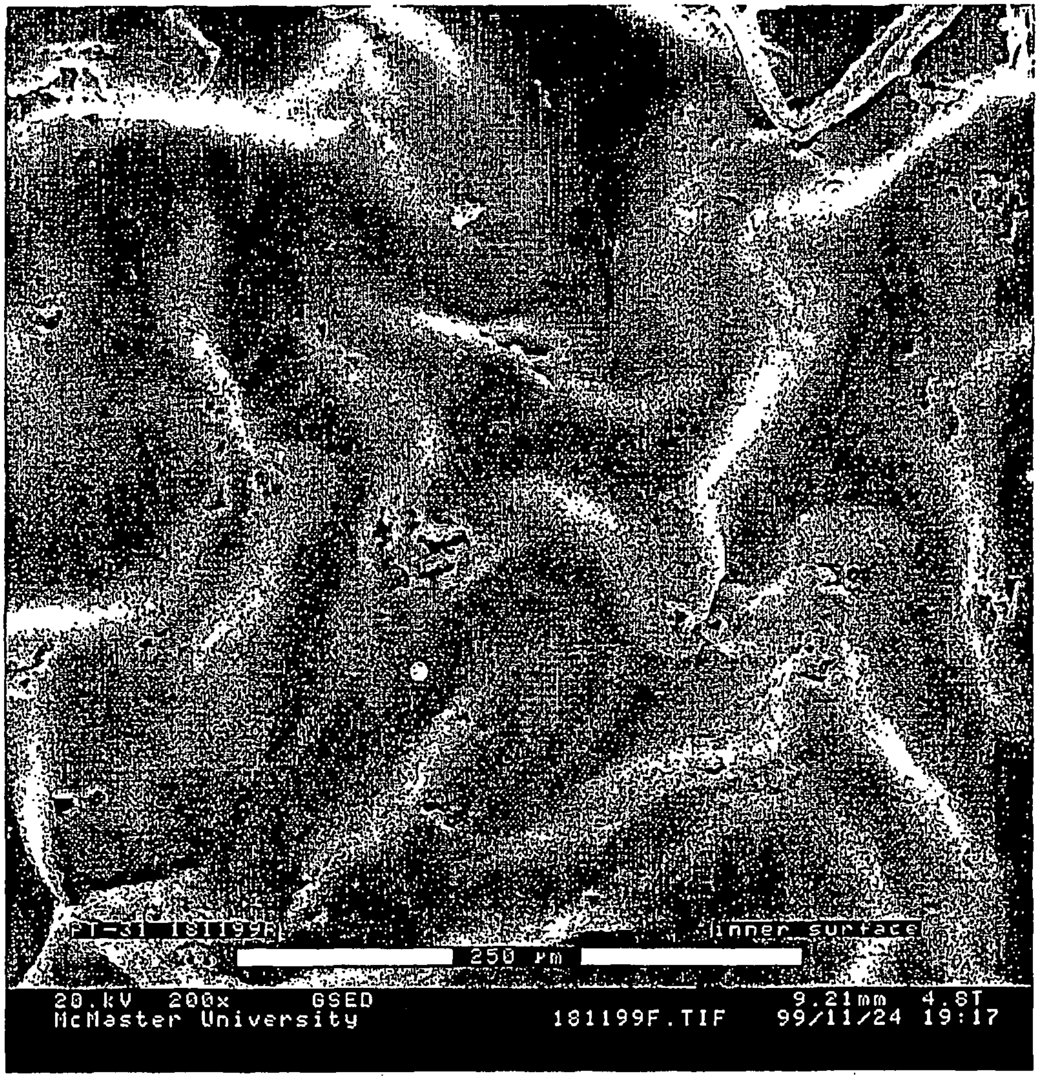

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Fig.15

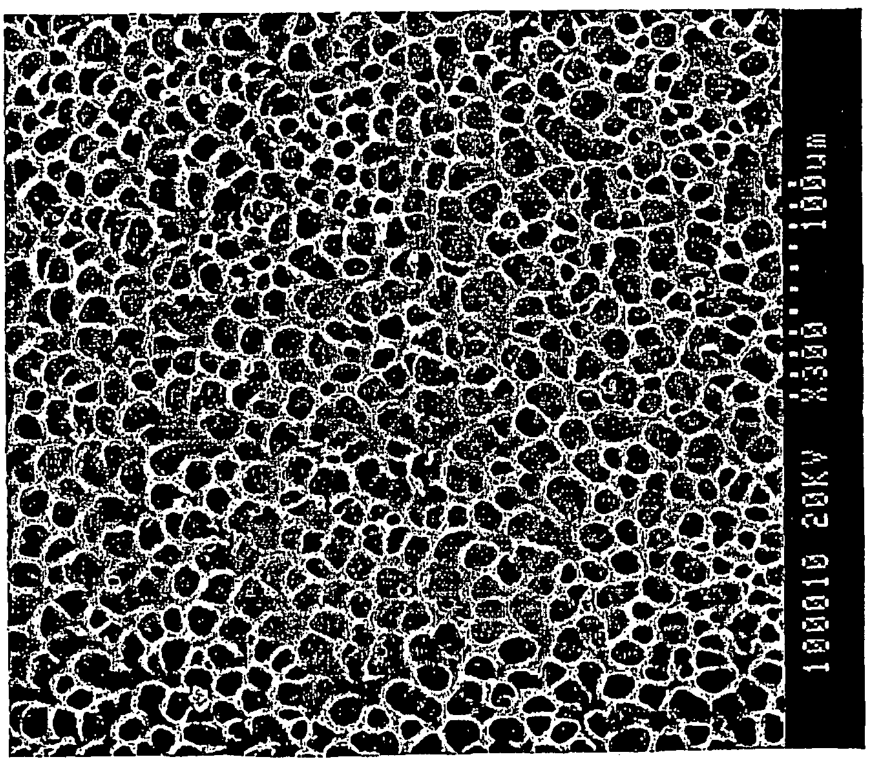

Fig.16a

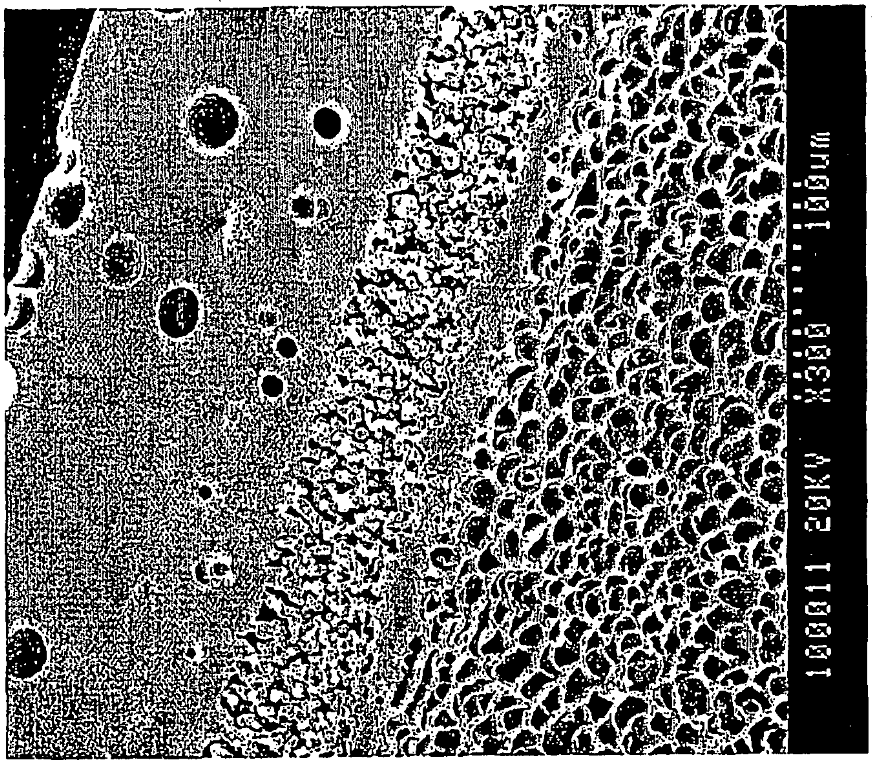

Fig.16b

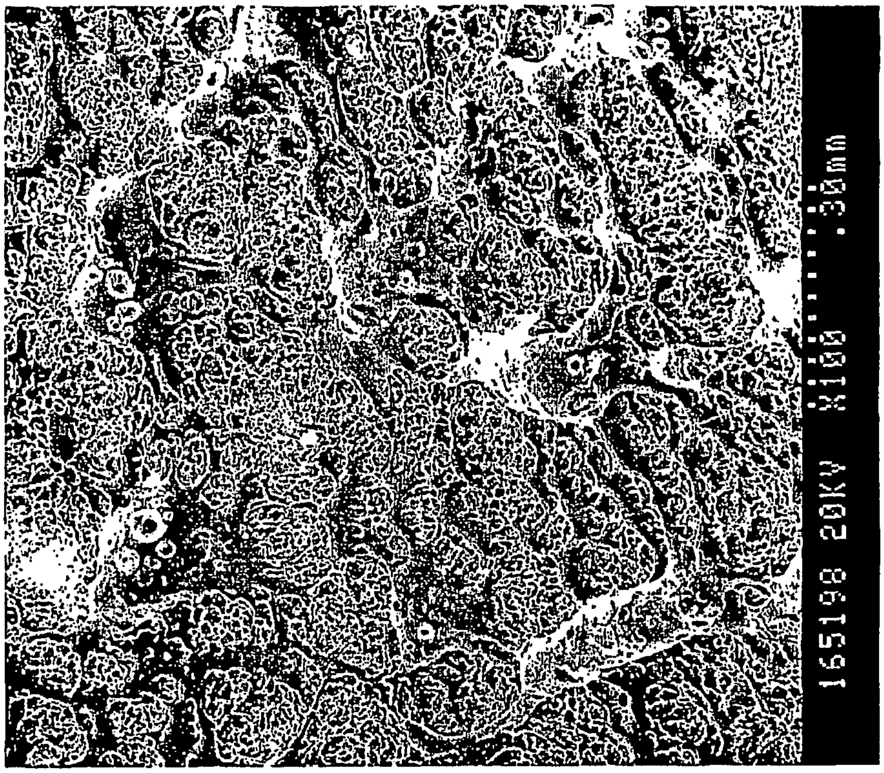

Fig.17b

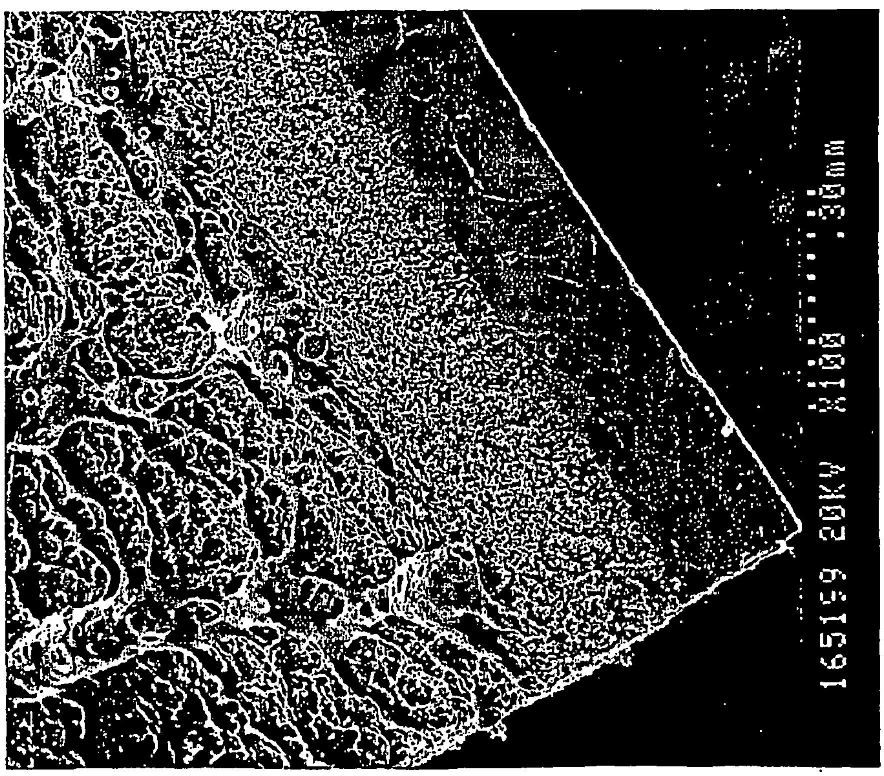

Fig.17a

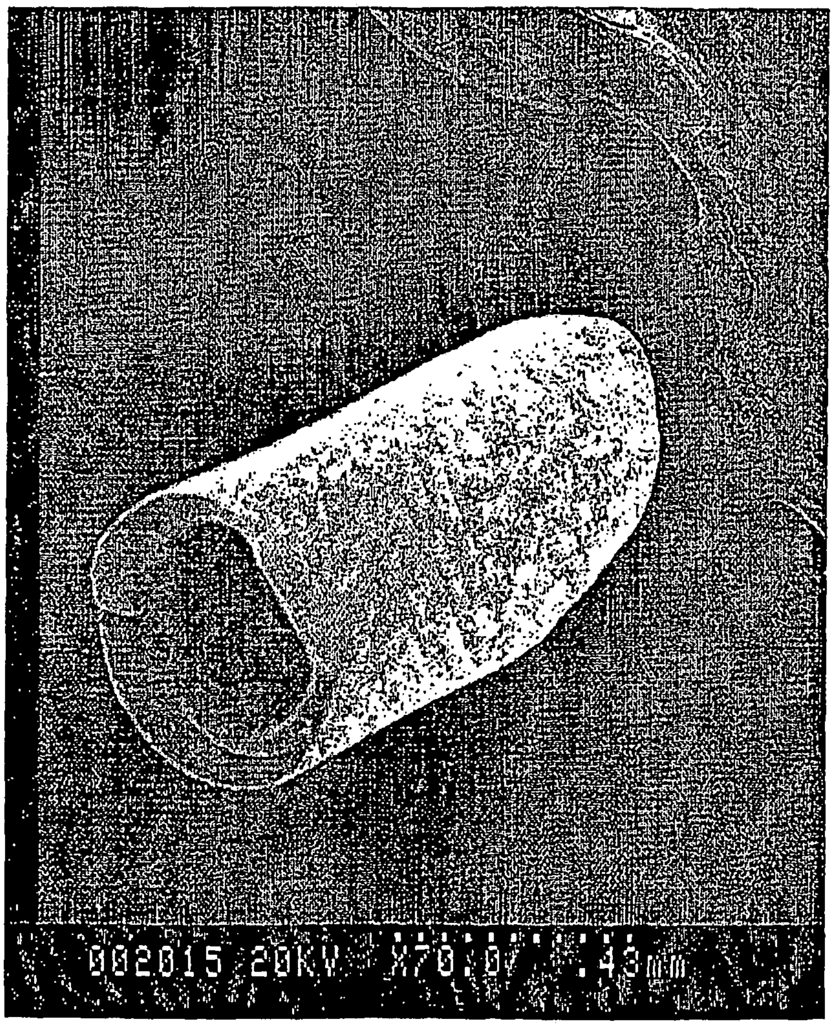

Fig.18

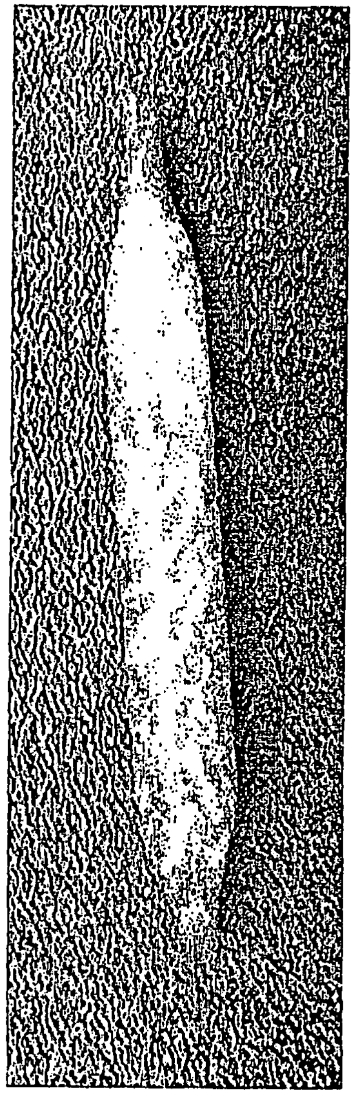

Fig.19